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U.S. EPA/EC Joint Project on the Evaluation of (Quantitative) Structure Activity Relationships

US EPA / EC JOINT PROJECT ON THE EVALUATION OF (QUANTITATIVE) STRUCTURE ACTIVITY RELATIONSHIPS

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Final Report

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Contents

1. Background

In October 1989 the OECD organized, in the context of that organizations chemicals programme, a workshop on notification schemes for new chemicals. The major objective of this meeting was to review, in the light of the 1981 OECD Council Act on the Mutual Acceptance of Data, the notification schemes applied by the Member Countries of the OECD. The 1981 Council Act recommended that countries require manufacturers/importers to supply a certain minimum pre-marketing data set (MPD) before placing a new chemical substance on the market: the test data to be generated experimentally using standard OECD testing guidelines.

From the information presented at the workshop, it was apparent that the majority of Member Countries had introduced notification schemes based on the principle of an MPD although the content of the testing package often diverged from that recommended in the Council Act. One notable exception to this general tendency was, however, the United States of America where the notification scheme for new chemicals established under the 1976 Toxic Substances Control Act (TSCA) did not, a priori, oblige manufacturers/importers to carry out testing before placing a new substance on the market. Essentially, the scheme established under TSCA required the submission of available data, often extremely limited, to the regulatory authority, in this case the Environmental Protection Agency (EPA). Faced with this paucity of experimental data, the EPA were obliged to place increasing reliance on techniques known collectively as (Quantitative) Structure Activity Relationships (Q)SAR, in order to carry out a preliminary hazard/risk assessment of notified substances: (Q)SARs are predictive methods which estimate the properties (activity) of a chemical e.g. melting point, vapour pressure, toxicity and ecotoxicity, on the basis of its structure.

One of the most important recommendations from the OECD workshop was that an attempt be made to evaluate the predictive power of the (Q)SAR, used by the EPA. It was in addition recommended that this evaluation be achieved by applying the (Q)SAR methods to chemicals for which extensive test data were already available and then comparing the properties predicted by SAR with the properties observed from experimental testing.

In the European Community, a new chemicals notification scheme came into force in 1981 in accordance with the rules laid down in Directive 79/831/EEC, being the sixth amendment to Directive 67/548/EEC on the classification, packaging and labelling of dangerous substances. The notification procedure required manufacturers/importers to submit a standardized data set (roughly similar to the OECD MPD) with experimental data being generated according to prescribed test methods (essentially equivalent to OECD test guidelines). By 1989, the EC notification scheme had been in force for over 8 years and several hundred notifications had been received. The OECD workshop therefore recommended that the predictive power of the (Q)SAR methods used by the EPA should be evaluated against the data submitted on chemicals in the context of the notification scheme established in the European Community.

The recommendations from the OECD workshop were therefore the starting point for the collaborative project between the European Community and the United States of America, which is described in this report. It must be emphasized that the scope of this project was limited to that defined by the OECD workshop namely: an evaluation of the predictive power of the (Q)SAR techniques used by the EPA in the context of the new chemicals notification scheme established under the Toxic Substances Control Act. The project is not, and was not designed to be, an evaluation of QSAR techniques in general.

N.B. : New chemicals notification schemes in the United States of America and the European Community. In order to understand fully the design of the collaborative project, its implementation and the conclusions which can be drawn from it, it is essential to understand the details of the notification schemes as they are applied in the United States of America under the Toxic Substances Control Act and in the European Community under Directive 67/548/EEC as amended. Descriptions of the schemes are to be found in chapter 3 of this report.

2. Project Design

2.1. Competent Bodies

In the United States of America, the Agency responsible for processing the new chemicals notifications and the body responsible for the realization of this collaborative project is the Environmental Protection Agency.

In the European Community, each of the 12 Member Countries has designated national Competent Authorities responsible for the implementation of the notification scheme established under Directive 67/548/EEC as amended. The Commission of the European Communities is also involved in the implementation of the notification scheme as well as being responsible for ensuring co-ordination between the Member States. For the purposes of this project, the Commission of the European Communities was mandated by the national Competent Authorities to act as the contact point with the EPA. For the detailed realization of the project the input from the EC was co-ordinated by the Commission with advice and support from the national Competent Authorities.

Lists of the EPA and EC experts who were responsible for carrying out the detailed analyses upon which this report is based, are included as Annex 1.

2.2. Confidentiality

Directive 67/548/EEC, as amended, makes clear that the confidential data included in a notification dossier can only be made available to the national Competent Authorities designated as being responsible for implementing the Directive, and the European Commission. Within the national Competent Authorities and the Commission only a restricted number of staff are allowed access to this confidential information and extensive measures are taken to ensure the physical security of this information.

Given the obligations imposed under the Directive, the confidential data submitted to the European Authorities could not be made available to the EPA without the specific permission of the manufacturers/importers who had submitted the notifications in Europe. Therefore, prior to the start of the project, the national Competent Authorities in the EC Member States wrote to all notifiers asking for permission to release confidential data to the EPA for the purpose of this collaborative project. It was made clear to the notifiers that the EPA had undertaken to accord the same degree of protection to confidential data submitted under this project as they would to confidential business information submitted as part of a new chemical notification under TSCA.

A total of 107 companies responded positively to the request made by the national competent authorities. A list of these companies is attached as Annex 2 to this report. The EPA, the national Competent Authorities and the European Commission would like to thank these companies for their assistance without which this project could not have been carried out.

Confidential information, exchanged between the EPA and the European authorities was taken by hand from the notification unit located in Direction General XI of the European Commission in Brussels to the mission of the United States of America to the European Commission. From there the information was transferred by diplomatic bag to the EPA in Washington. While in the EPA the data were held in secure areas dedicated to the storage and processing of confidential business information. At the end of the project, confidential documents supplied to the EPA were destroyed.

2.3. How the project was organized

Discussions with EC notifiers regarding the release of confidential data to the US authorities were completed by December 1990. All together, companies gave permission for information, on a total of 175 substances to be included in the project. Chemicals were removed from the study if, for example, they were on the original TSCA inventory or had been submitted under the US notification scheme and had been accompanied by the equivalent of the MPD. This reduced the test set of chemicals to a total of 144. The various use categories of substances notified under the EC scheme were reasonably well represented in this set of 144. The dates of notification ranged from 1983 to 1990. For the US, however, the scarcity of polymers and the inclusion of pesticides and pharmaceutical intermediates represents a somewhat atypical data set of chemicals and, as such, may not have been as good a match with the US experience as could be desired.

In autumn 1991, DG XI of the European Commission communicated to the EPA the following information in relation to each of the substances selected for the study :

- IUPAC name
- CAS number (where available)
- physical form
- melting point
- use (where this was adequately described in the original dossier).

Prior to the dispatch of information, the Commission and the national competent authorities were provided by the EPA with details of the (Q)SAR methods that the EPA would use during the collaborative project.

The EPA treated this input data in exactly the same way that they would have treated data submitted under the TSCA new chemicals notification scheme, applying (Q)SARs to predict the properties of the chemical and carrying out a preliminary hazard assessment. For each substance the EPA drew up a one/two page summary of their analysis. These summaries were delivered to DG XI of the EC Commission in March 1992 and thereafter to the national competent authorities.

In April 1992, DG XI communicated the full test dossiers on each of the 144 substances to the EPA.

Between April 1992 and September 1992 the US EPA on the one hand and the EC Member States/Commission (DG XI) on the other reviewed and analysed the result of the study. Between 14-16 October 1992, a joint meeting of US and EC experts took place at the Umweltbundesamt in Berlin to discuss the results of the project. Following that meeting, this final report was prepared for onward transmission to the OECD.

3. Notification schemes in the European Community and in the United States

3.1. Essential features of the notification scheme for new chemical substances in the European Community

- **Overview/Legal basis**

The new chemicals notification scheme is established within the framework of Directive 67/548/EEC on the classification, packaging and labelling of dangerous substances. The notification scheme was in fact introduced in the 6th amendment to the basic Directive (Directive 79/831/EEC) which came into force in the EC Member States in 1981. [A copy of the sixth amendment is attached as Appendix 1].

The obligation to submit a standard notification dossier harmonised at the level of the EC falls upon any manufacturer or importer wishing to place a new substance on the market in quantities greater than 1 tonne per annum per manufacturer. [Notice that the EC scheme is a pre-marketing scheme and not premanufacture as is the case in the United States.]

A "new substance" is defined as one that is not to be found on the European Inventory of Existing Commercial Chemical Substances (EINECS). EINECS contains over 100,000 chemicals on the EC market before 18th September 1981.

Even if a chemical is new it may not need to be notified if it falls into one of the exempted product sectors e.g. pharmaceuticals, or substance classes e.g. polymers containing "old" monomers, which are specified in Articles 1 and 8 of the Directive respectively.

Notifiers are required to submit a notification dossier relating to the substance as marketed, including any impurities and additives necessary for keeping the substance stable but without separable solvent. This means that the substance or entity assessed is very rarely a pure substance and indeed some of the properties observed may be due to the impurities or additives present in the "substance". This means that the assessment is made on the entity to which man or the environment will actually be exposed rather than on the pure substance.

- **Information to be provided by the notifiers**

Notifiers must submit a notification dossier including an extensive technical dossier containing the results of the experimental testing carried out on the substance. The contents of the technical dossier are laid down in Annex VII to the Directive. This standard testing package is known as the "base set" test dossier. When the marketing levels for a substance reach 10 tonnes per annum per notification the authorities may require further testing. When marketing levels reach 100 tonnes and 1 000 tonnes per annum the notifier is required to carry out further testing. These obligatory supplementary testing packages are known as the level 1 and level 2 testing packages respectively and are laid down in Annex VIII to the Directive.

The testing methods to be used in carrying out testing of chemicals for the purpose of notification are laid down in Annex V to the Directive.

The "base set" test package is approximately equivalent to the OECD Minimum Pre Marketing Data Set (MPD) and the testing methods in Annex V are, for the majority of tests, equivalent to the corresponding OECD test guidelines. Requiring testing according to agreed standard test methods has the distinct advantage of facilitating comparison of substances.

- **How does the notification scheme work ?**

The notifier submits a notification dossier to the competent authority in the Member State where the substance is manufactured or imported. Forty five days after the authority is in receipt of a dossier which conforms to the Directive, the notifier can place the substance on the market anywhere in the European Community.

The authority receiving the notification prepares a summary dossier which is circulated through the Commission in Brussels to the other eleven Member States (a copy of the summary dossier is attached as Appendix 2).

The other Member States and the Commission can request the lead authority to make changes to the dossier or ask the notifier for further information.

The essential feature to note about the notification scheme is that it is a de-centralized one: the lead authority effectively takes the decision as to the acceptability of the notification dossier on behalf of the rest of the Community. In order for this de-centralized approach to work effectively the degree of flexibility/subjectivity which the system can tolerate is rather small: it is not one single group of people which take the decisions but 12 different national authorities each acting alone with the Commission playing the role of co-ordinator. This is one of the main reasons for the perceived rigidity in the EC notification scheme which is based upon a fixed set of information which must be supplied for each substance. This loss of flexibility is one of the costs to be paid for the benefit of having a notification scheme which has worked effectively across 12 different countries for over 10 years.

- Classification and Labelling

Directive 67/548/EEC as amended contains detailed and extensive rules for the classification and labelling of dangerous substances. Substances are classified on the basis of objective, often very precise, criteria which are laid down in Annex VI to the Directive (the version of Annex VI in force at the time of this study is included as Appendix 3). The classification criteria are in turn based upon the results of the tests carried out on the substance. The rules laid down in Annex VI also determine whether the labelling of a substance should carry a pictogram/symbol indicating certain types of danger and also whether the label should indicate certain standard phrases describing the risk of the substance, so called R-phrases, as well as certain standard phrases describing how the substance can be used safely, so called S-phrases.

In addition to determining the labelling of a substance, the classification is the starting point for the risk assessment in the European Community and also drives downstream legislation concerned with aspects of risk management, e.g. worker protection.

As can be understood from the short description given above, classification and labelling, and in particular classification, are central elements in the EC chemicals legislation. However, the criteria for classification are often extremely precise, for example, substances are classified as "very toxic" if the acute oral LD50 is less than or equal to 25 mg per kilogram but as "toxic" if the value is above 25 mg but less than or equal to 200 mg per kilogram. Classification schemes which demand such a high degree of precision to discriminate between substances allocated to one category or another obviously demand a high degree of precision in the estimates made of the chemical's properties. Experimental testing does generate precise values and even though this precision may be more apparent than real, it does provide an effective basis for building an objective classification scheme. (Q)SAR methods on the other hand usually generate less objective/precise estimates of chemical properties, and therefore do not immediately lend themselves as input data constructing classification schemes.

3.2. Essential features of the notification scheme for new chemical substances in the United States

- **Overview/Legal basis**

Persons who plan to manufacture or import a new chemical substance for a commercial purpose are required to provide the Environmental Protection Agency (EPA) with a premanufacture notification (PMN) at least 90 days prior to the activity. Section 5 of the Toxic Substances Control Act (TSCA) was designed to enable the Agency to review activities associated with manufacture, processing, use and disposal of any new chemical substance before it enters the market place. If necessary, EPA is empowered to take action to prevent unreasonable risks before they occur (pollution prevention at its basic level). This is accomplished by requiring premanufacture reporting. [A copy of the relevant part of the TSCA is attached as Appendix 4].

TSCA defines "new chemical substances" as chemical substances not listed on the TSCA Chemical Substance Inventory and not otherwise excluded by the regulations. The Inventory includes chemicals in commercial production between 1975 and 1979, and any chemicals reviewed in the PMN program which have subsequently been commercially produced. The Inventory currently contains over 70,000 chemical substances, of which over 7,500 substances have been added to the Inventory through the submission of notifications of commencement to manufacture (NOCs) after those substances had completed the PMN review process and were manufactured for commercial purposes.

The PMN program has been in place since 1979 and, through fiscal year 1992, has reviewed over 21,500 notices. The Agency took action to protect health and the environment from potential risks posed for over 1,800 of these new substances.

- **The PMN review process**

EPA developed the PMN review process to meet the statutory mandate of TSCA §5. Under the US Program, any person who intends to manufacture or import a new chemical substance is required to provide to EPA available data on the chemical structure, production, use, release, exposure, and health and environmental effects. However, section 5 does not require chemical companies to test their new chemical substances for potential toxic effects. Therefore, EPA's review (and 5(e) regulatory actions) are often conducted in the absence of data. The Agency relies on Structure Activity Relationships (SAR) to make predictions concerning the environmental fate and effects (health and environmental) of PMN chemicals. Each PMN proceeds through a screening process to determine whether more detailed review is required and to identify candidates for regulatory action. The Structure Activity Team (SAT), made up of a multidisciplinary group of experts, is responsible for the initial assessment of fate and effects. EPA focuses on the relatively few new chemicals of greatest concern--those which are structurally related to known toxic chemicals, and those about which little is known.

a. Initial screen. PMN notices go through a multidisciplined initial review designed to ascertain whether regulatory action on a more detailed analysis is warranted. Preliminary chemistry, Structure Activity Relationship (SAR) analysis, exposure, and environmental fate analyses are conducted.

b. Use of SAR in hazard assessment. Given the qualitative and quantitative limitations of the test data provided with PMNs (over half of all PMNs contain no test data), EPA has developed innovative approaches to characterize the potential hazards associated with new chemical substances. The major components of EPA's SAR-based approach to hazard analysis are the following:

- critical review of submitted test data, if any, on the PMN chemical;

- identification and selection of potential analogues and/or prediction of key PMN metabolites, followed by critical review of test data available on these chemicals;

- use of QSAR (Quantitative Structural Activity Relationships) methods when available and applicable; and

- the experience and judgement of scientific assessors in interpreting, weighing, and integrating the often limited information yielded by the above hazard analysis components.

The TSCA PMN reporting requirements can be compared with the European Community's (EC) "premarketing" notification requirements. As the terms indicate, premanufacture notification under TSCA is required at an earlier point in the development of a chemical than is the case for the EC's premarket notification procedure. Many of the information reporting requirements under the EC directive are similar to those in TSCA with the major difference that the EC directive requires, as a mandatory part of the notification, a specified "base set" of health, environmental, and physical chemical test data. Therefore, a minimum set of test data is available on premarket notification EC chemicals, whereas the hazard assessment of TSCA PMN chemicals often starts out with fewer or no data.

c. Cases completing their initial review are brought to the first regulatory decision meeting called "Focus". At this meeting, the results of the Initial Screen analyses are presented and considered and a decision rendered on each PMN case. The possible outcomes include: drop the case from review; hold it over for more investigation (standard review); or move directly toward a regulatory outcome for certain standard categories of chemicals. To date, the Agency has developed over 35 chemical "categories of concern" to facilitate the new chemicals review process.

d. For chemicals which are not screened out early, the standard review includes:

- Conducting a chemistry analysis,
- Identifying structurally analogous substances,
- Searching the literature for toxicity data,
- Analysing test data on the substance or analogous substances,
- Analysing potential releases to the environment,
- Estimating exposures to workers and the general population,
- Estimating potential concentrations in surface waters,
- Investigating additional uses which could significantly alter exposure.

e. Cases completing standard review are taken to the PMN Disposition Meeting for a final decision. The meeting can result in a decision to drop a case from further review, to regulate (and require controls) under section 5(e) or 5(f) (see below), or to "ban" the substance pending the receipt and evaluation of "upfront testing."

f. If a regulatory decision to impose certain controls on the manufacture, process, use, distribution, or disposal of a new substance is reached, EPA staff communicate and negotiate with the submitter. Similarly, if "upfront" testing is recommended in face of banning the new substance, this decision is also communicated to the submitter by EPA staff.

g. Notice of Commencement (NOC) of Manufacture or Import. An NOC must be submitted within 30 days of commencement of commercial production of a chemical substance which has completed the 90-day review period. The substance is then added to the TSCA Inventory.

Regulating new chemical substances under TSCA

Section 5(e) and 5(f) of TSCA authorize EPA to prohibit or limit the manufacture, processing, distribution in commerce, use, and disposal of a new chemical substance if EPA makes the following determinations:

a. Section 5(e) findings:

- Available information on the substance is insufficient to permit a reasoned evaluation of its health or environmental effects; and

- (1) The manufacture, processing, distribution in commerce, use, or disposal of the substance may present an unreasonable risk of injury to health or the environment (referred to as a "may present" or risk-based determination); or

- (2) the substance will be produced in substantial quantities and (A) may reasonably be anticipated to enter the environment in substantial quantities, or (B) there may be significant or substantial human exposure (referred to as an "exposure-based" finding). An exposure-based review is triggered by an estimated threshold production volume of 100,000 kilograms per year. For those substances meeting significant or substantial human exposure criteria, chemical manufacturers may be asked to perform some or all of the following tests on their PMN substance: an Ames assay, an in vivo mouse micronucleus test, a 28-day (oral) repeat dose toxicity test and an acute oral toxicity test. PMN substances meeting the environmental release criterion may be tested for algal acute toxicity, daphnid acute toxicity, and fish acute toxicity. Additional elements of the exposure-based testing policy may include environmental fate testing and, for PMN substances having higher production volumes, developmental toxicity testing requirements.

b. Section 5(f) findings:

- There is a reasonable basis to conclude that the manufacture, processing, distribution in commerce, use, or disposal of the substance will present an unreasonable risk of injury to human health or the environment before a TSCA §6 rule can be issued to prevent the risk (referred to as a "will present" determination):

- A section 5(f) rule, which limits activities involving a new substance, is a section 6(b) proposed rule which is immediately effective upon proposal. A section 5(f) order prohibits all activities involving the substance. (To date, EPA has issued 3 section 5(f) rules and no section 5(f) orders, although a number of PMNs have been withdrawn from review after EPA notified the submitters that the Agency intended to ban the substances)

c. Practices under section 5(e):

To date, there have been five outcomes, depending upon the facts of the case, when EPA has made a determination under section 5(e):

- The company may withdraw the PMN.

- The company may develop toxicity information sufficient to permit a reasoned evaluation of the health or environmental effects of the substance prior to the conclusion of the review period ("upfront" or "voluntary" testing). Where exposures or releases cannot be controlled pending testing to address EPA's concerns, or the requested testing is relatively cheap and not very time-consuming, this may be the only option available to the PMN submitter short of withdrawing the PMN.

- The company may develop and provide to EPA other information on the potential effects of the substance or its analogues, the potential exposures, or both, which if accepted by the Agency, would negate the potential unreasonable risk determination.

- The company may, together with EPA, suspend the notice review period, and negotiate and enter into a section 5(e) Consent Order. The Consent Order would permit limited manufacture, processing, distribution in commerce, use, and disposal of the substance pending the development of information. A Consent Order may contain a requirement that toxicity data be submitted to EPA when a specified volume of the chemical has been produced. This production volume level is set where EPA estimates that profits from the chemical will support the cost of testing.

- The company may refuse to withdraw the PMN, negotiate a Consent Order with EPA, and/or conduct up-front testing or develop other information. EPA would then unilaterally develop a Proposed Order, under the procedures in section 5(e), to ban manufacture or import.

4. Results

4.1. Introduction

For this project, the test set of chemicals was comprised of a maximum of 144 substances (sometimes fewer depending upon the end-point and the results available). Each substance was assigned a number and is referred to in the report by means of that number. A short generic description of each substance included in the project is given in Annex 3.

In the sections which follow, the results are generally presented in a summary form, not substance by substance. However, detailed annexes presenting the results by end-point and by substance are appended to the report.

4.1.1. Evaluation criteria

For each end-point, specific criteria were agreed between the US and EC experts for assessing the "success", "failure", "hit-rate" of the (Q)SAR methods, e.g. for most physico-chemical and the ecotoxicity data, agreement was defined as being reached, if the difference between measured and predicted value did not exceed a factor of 10. In addition to these end-point specific criteria the following, more general, considerations were also taken into account in relation to each end-point.

- Can the predicted data be used on a one-to-one basis in the place of the test results foreseen in the OECD Minimum Pre-Marketing Data Set (MPD) or other similar test based notification schemes?

- Can the results of the predictive approach be used in the context of schemes for the classification and labelling of chemicals, which employ predefined cut off values?

- If estimated values based on predictive methods are used instead of test data for the purposes of preliminary hazard assessment, are the predictive methods sufficiently reliable in relation to each end-point and what is the likelihood of false negatives in relation to each end-point?

- The OECD MPD and other test based systems for screening of new chemicals frequently do not include important end-points. To what extent do predictive methods allow one to go beyond the scope of fixed data sets and to assess additional end-points?

4.1.2. Complicating factors

Issues addressed with regard to each end-point are discussed in connection with that end-point. Nevertheless a number of common problems can be identified which complicated the comparison of predicted and observed results in relation to all end-points.

- Pure substances vs notified substances

In the EC notification scheme substances are notified essentially as they are marketed including impurities but minus any separable solvent. This means that impurities or non-separable solvents may contribute significantly to the observed properties. In contrast, the (Q)SAR methods are based on pure substances and impurities are only taken into account in the US system if the manufacturer is aware of their existence/identity and reports this information to the EPA.

For the above reason the (Q)SAR methods will often fail to predict properties which are due to the presence of impurities.

- **Effect quantification**

Experimental data reported from the EC notification dossiers may display considerable variability (extremely wide confidence limits). Furthermore, both predicted and experimental data were often expressed as $>n$, or as $<n$ or as ranges. In these cases agreements had to be reached end-point by end-point as to how to make effective comparisons.

- **End-point selection**

When considering properties such as acute aquatic toxicity or biodegradation the precise end-points addressed by the experimental testing and the (Q)SAR predictive methods were sometimes different e.g. 24 hour toxicity as opposed to 48 hour; "ready biodegradability" as opposed to an estimate of the time required for complete biodegradation. Again in such cases, agreement had to be reached on a realistic basis for comparison.

- **Descriptive narrative assessment vs numerical data**

(Q)SAR methods frequently generate predictions placing substances in concern categories such as low, medium or high. Again agreement had to be reached as to how such predictions should be compared with an objective value such as a numerical (e.g. 35 mg/kg bodyweight/day) Lowest Observed Adverse Effect Level (LOAEL) in a 28-day repeated dose toxicity study.

- **Nominal vs measured concentrations**

Test results for aquatic toxicity test, in the EC notification dossiers, particularly dossiers received early in the life of the notification scheme, were frequently based upon nominal rather than measured substance concentrations. In such cases it is entirely possible that the predicted value for aquatic toxicity generated by (Q)SAR is nearer to the "real value" than the result reported from the experimental determination.

4.2. Detailed analysis of results

A detailed description of the end-point by end-point comparison of the values predicted by (Q)SAR and the values generated by experimental determination in the EC notification dossiers is given below. For ease of presentation the abbreviations "EC" or "EPA" have been used as a convenient short-hand to identify the approaches used in the European Community and the United States Environmental Protection Agency respectively.

4.2.1. Physico-chemical and environmental fate parameters

4.2.1.1. Boiling point

For predicting the boiling point, the EPA experts use estimation methods, e.g. PCGEMS (Meissner's method), data on analogues and experimentally determined data obtained from the published literature investigations. Impurities are in general neglected in the predictions. The application of the estimation techniques was not possible for all the chemicals within this study.

Even though the boiling point is required for notified chemicals at "base set" level in the EC, for many substances in this study experimentally determined boiling points were not available as it was technically not possible to conduct the tests.

The boiling point is used to characterize the material, it is not directly used for risk or safety evaluations. The boiling point may serve as an input parameter for estimating vapour pressure, if the latter is unavailable from experiment.

Only for 30 chemicals out of the 144 were measured/estimated boiling point values available for comparison. The following criteria were applied for the analysis:

- for all values assigned with $< n$ or $> n$ the signs are deleted and the values are directly compared;
- the values are considered to be in agreement if the difference between calculated and measured data does not exceed $\pm$ 50 degree C.

The comparison of the SAR and MPD data is given in Table 1; for detailed analysis of the boiling point data see Annex 4.

TABLE 1: Comparison of boiling point data

	N° of chemicals	%
Total	30	100
Agreement	15	50
Disagreement	15	50

If the literature data were included in the analysis, an additional 11 chemicals would be added, for which the US boiling points were all in agreement with the EC data. The agreement was below 50% for solid substances.

- Conclusions

The data set for analysis was very small, so only limited conclusions are possible. The boiling point is not used directly in the hazard/risk assessment nor is it used in the classification schemes. On the other hand, the boiling point is a basic piece of information about a chemical which manufacturers should normally be aware of; furthermore boiling point determination by testing is relatively inexpensive. Thus, it is concluded that it is preferable, in the EC scheme, to continue to measure the boiling point when it is technically possible to do so.

4.2.1.2. Vapour pressure

The vapour pressure of the chemicals under consideration is predicted by the EPA using methods based on the Antoine equation or the Watson equation or by applying the PCNOMO-technique. The vapour pressure contributes indirectly to the EPA's risk assessment, as it is used as an input parameter to the exposure and fate analysis.

Also within the EC risk assessment, the vapour pressure serves as a basic parameter for human health and environmental exposure evaluation. Measured vapour pressure data are required at "base set" level in the EC; however, calculation methods can be used according to Annex V for range finding purposes, for justifying the non-performance of the test or for providing an estimate or limit value in cases where the experimental method cannot be applied due to technical reasons (including where the vapour pressure is very low) .

For 113 chemicals out of the 144 test chemicals measured data on vapour pressure were available, and predictions were available for all chemicals. The predictions are given in the majority of the cases as upper/lower bounds. In order to compare the SAR values with the measured data, all values were converted to like units (torr). The following criteria for comparison analysis were applied :

- for all values assigned with $< n$ or $> n$ the signs are deleted and the values are directly compared;
- the lower limit is set at 10^{-6} torr. All SAR and MPD values that are less than this value are arbitrarily set to 10^{-6} torr;
- the values are considered to be in agreement if they are within $\pm$ 1 log unit.

The results of the comparison of the SAR and MPD data are given in Table 2; the detailed analysis of the vapour pressure data is to be found in Annex 5.

TABLE 2: Comparison of vapour pressure data

	N° of chemicals	%
Total	113	100
Agreement ($\pm$ 1 log unit)	71	62.8
Disagreement	42	37.2
- of these, predictions which were not at all in agreement (>3 log units difference)	[23]	[20]

The data pairs which show big deviations were more rigorously investigated: in some cases the disagreement can be put down to the fact that the material used for the experimental determination contained volatile impurities, whereas the predictions are carried out for the pure substance.

- Conclusions

The best agreement was observed between the PCNOMO estimates and the measured values. In general the predictions tend to underestimate the vapour pressure. Assessing the deviations with respect to chemical classes is not possible with the small data set available. Imprecise predictions of very high or very low vapour pressure do not affect the overall assessment, but more precise values are needed in the decision-relevant range. Vapour pressure contributes to the exposure portion of the risk assessment in the EC and the US; however, it is not normally used for the purpose of classifying chemicals within the EC classification scheme. Under/overstimation of vapour pressure can result in an under/overestimation of the exposure associated with a chemical and thus contribute to an under/overestimation of the risks. The majority of methods for the experimental determination of vapour pressure are relatively inexpensive, and therefore notification schemes based upon testing will probably continue to require experimental determination. Schemes based upon predictive methods may need to be adjusted to foresee a more systematic approach to the experimental determination of this parameter for some of the chemicals which are identified as being of concern on the basis of a preliminary hazard/risk assessment.

4.2.1.3. Water solubility

The methods used by the EPA experts for predicting water solubility are based on log P_{ow} values (PCGEMS). However, most new chemicals do not match the application criteria of the available QSARs, e.g. applicability recommended for liquid substances or only for certain log P_{ow} ranges. Within the EPA hazard/risk assessment scheme, water solubility serves as an input parameter for the environmental fate analysis and ecotoxicity assessment. The lower prediction limit for fate and ecotoxicity assessment is ≤1 µg/l; for some other purposes it may be around 1 mg/l. In cases of concern, e.g. for chemicals with higher production volumes, measured water solubility is required.

In the EC, experimentally determined water solubility data, which are required at "base set" level, are also used in environmental exposure assessment; they may also contribute to the classification "dangerous for the environment".

Measured numerical values were not available for 13 of the 144 chemicals, as their determination was technically not possible, but in 6 cases out of the 13, qualitative test data were available which could be used for comparison. In 4 further cases the SAR data cannot be used for the comparative analysis. This means there were 133 data pairs for comparison. An additional problem affecting meaningful comparison is the lack of precision in the data (both predicted and measured): many data, in particular the majority of the predicted data, are given as ranges or upper/lower bounds, in case of measured data the values given as bounds are mostly without an indication of detection limit.

The following criteria were applied for the comparison analysis:

- for all values assigned with $<n$ or $>n$ the signs are deleted and the values are directly compared;
- for data given as ranges, the average is taken for comparison;
- the lower limit is set at 0.01 mg/l and the upper limit at 10,000 mg/l. All SAR and MPD values that are less than the lower limit value, or above the upper limit value are arbitrarily set to 0.01 mg/l or 10,000 mg/l, respectively;

- the values are considered to be in agreement if they are within ±1 log unit.

Results of the comparison between SAR and MPD data is given in Table 3, the detailed analysis of water solubility data in Annex 6.

TABLE 3: Comparison of water solubility data

	N° of chemicals	%
Total	133	100
Agreement (± 1 log unit)	90	67.7
Disagreement	43	32.3

A rigorous scientific analysis of the estimated and measured data for water solubility was not possible due to the imprecise nature of both data sets. Tendencies of over or underestimation of water solubility are not observed. A relatively high rate of disagreement is detected for low solubility values (< 1 mg/l).

- Conclusions

Water solubility is a significant parameter in risk assessment and might have a decisive impact on the classification "dangerous for the environment". Under/overestimation of water solubility can result in a under/overestimation of exposure and thus contribute to a under/overestimation of the risks. SAR based predictions may not always be of sufficient reliability, especially in the range of low solubility, i.e. < 1 mg/l, due to the complexity of factors influencing a chemical's water solubility. The experimental determination of water solubility is relatively inexpensive, therefore notification schemes based upon testing will probably continue to require experimental determination. Schemes based upon predictive methods may need to be adjusted to foresee a more systematic approach to the experimental determination of this parameter for chemicals at higher production levels or which are identified as being of concern for the aquatic environment on the basis of a preliminary hazard/risk assessment.

4.2.1.4. Partition coefficient

The partition coefficient is a key parameter to evaluate a chemical's impact on the environment.

Furthermore, its particular importance is underlined as, in the SAR methodologies, several other predictions, e.g. ecotoxicity/toxicity, are based upon it. The SAR prediction methods applied by the EPA use the MedChem ClogP Software package; the respective estimations are based on a fragment method. In cases of missing fragments, their values are estimated from expert knowledge. The upper prediction limit applied by the EPA for fate assessment is log P_{ow} ≥6. For ecotoxicity assessment no upper limit is considered for some chemical classes.

In the test driven, stepwise assessment scheme of the EC, the partition coefficient is also used in the decision taking process on further testing (e.g. for bioaccumulation potential); in addition, the log P_{ow} contributes to the criteria for classification as "dangerous for the environment" within the EC classification scheme: the log P_{ow} value 3 represents the cut off value for decisions on further testing and for classification. The EC notification scheme requires experimentally determined partition coefficient data at "base set" level. Nevertheless, Annex V recommends to estimate log P_{ow} for

deciding which of the experimental methods is appropriate, for selecting appropriate test conditions and for providing a calculated log P_{ow} in cases where the experimental methods cannot be applied for technical reasons. Therefore, in a number of cases, only estimated values were available in the EC dossiers. Those values were not taken into consideration for the comparative analysis of the SAR/MPD data.

Eighty two chemicals with both measured and predicted log P_{ow} values are available for the comparative study. The analysis included the application of the following criteria for comparison :

- for all values assigned with $<n$ or $>n$, the values are directly compared;
- for values given as ranges, the arithmetic average is used;
- the lower limit is set at log $P_{ow} = 0$, all values that are below 0 are arbitrarily set to 0;
- the upper limit is set to log $P_{ow} = 6$; all values above 6 are arbitrarily set to 6;
- the values are considered to be in agreement if they are within $\pm$ 1 log unit.

The results of the comparison of the SAR and MPD data are given in Table 4 , the detailed analysis of log P_{ow} is attached (see Annex 7).

TABLE 4: Comparison of partition coefficient data

	N° of chemicals	%
Total	82	100
Agreement ($\pm$ 1 log unit)	50	61
Disagreement	32	39
- Overestimation	25	30.5
- Underestimation	7	8.5

- Conclusions

The log P_{ow} estimates are in general reasonably accurate. However, estimations are in poor agreement for certain classes of compounds (e.g. dissociated compounds, charged compounds, surfactants, chelating compounds, organometallics, organophosphorous compounds, compounds with unknown fragment values, UVCB compounds) and are not applicable for them. Calculated log P_{ow} values above 4 tend to overestimate. Calculations in the range of 0 - 2 possibly underestimate log P; however, the data set available is too small for exhaustive analysis. The EPA calculation methods are in general successful at calculating log P values <0.

The results of this exercise indicate that the predictive methods for log P_{ow} may be of further importance in the EC in future, i.e. submission of predicted log P_{ow} values by the notifiers instead of measured data might be regarded as a possible option. However, the log P_{ow} range around the value 3, which is of particular importance for the EC classification and stepwise risk assessment scheme, will anyhow have to be taken into special consideration and may continue to require experimental determination as well as in the case of suspected underestimation.

4.2.1.5. Biodegradation

The data on this end-point were difficult to compare because different scales /definitions are used. The biodegradation estimates are given in semi-quantitative terms, indicating the appropriate time for complete degradation ("days", "days to weeks", "weeks", "weeks to months", "months" or "months or longer", whereas the OECD-based standard 28-days tests, which are available in the EC at "base set" level, result either in the decision "readily biodegradable" or "not readily biodegradable".

The EPA predictions concern biodegradability in terms of primary and ultimate biodegradability using structural analogies with previously studied chemicals. The applied estimation methods are based on expert judgement. The biodegradation predictions are used within the EPA risk assessment scheme as an important factor of the environmental fate analysis.

Biodegradation data are required in the EC for risk assessment and also for the classification "dangerous for the environment".

115 substances were available for comparison of predicted with experimental data. By relating estimates of "days" and "days - weeks" to the definition "readily biodegradable", 5 of the 9 substances experimentally determined as being readily biodegradable have been identified as such by the predicting methods (=55.5%). The other 4 readily biodegradable substances are predicted to degrade in "weeks", "weeks-months" or "months or longer". At the same time, for 4 substances which did not pass the experimental criteria for ready biodegradability, a rapid degradation was predicted ("days-weeks"). In general, as the predictive methods indicated increasing time required for complete degradation, the better they correlated with test results indicative of a lack of ready biodegradability. The overall results of the comparative study are summarised in Table 5, the detailed analyses of the data is to be found in Annex 8.

TABLE 5: Comparison of biodegradation results

Test result	Prediction	
	correct	incorrect
Total	107 (93%)	8 (7%)
Readily biodegradable	5	4
Not readily biodegradable	102	4

- Conclusions

The EPA methods are likely to identify those substances which are not "readily biodegradable", i.e. slowly degrading chemicals. However, they do not appear to work as well in identifying chemicals which readily degrade. The use of biodegradation predictions as a tool for establishing suitable testing strategies within a stepwise assessment scheme is considered a possible option for the future in the EC. On the basis of the EPA results it appears that if the predicted biodegradability is "weeks" or longer, testing for "readily biodegradability" would not be indicated. Instead a test for inherent degradability or another suitable test that provides further information on the biodegradation process should be carried out. If the predicted biodegradability is "days" or "days-weeks" corresponding to "readily biodegradability", then a "ready biodegradability test" would be needed for confirmation.

4.2.1.6. Hydrolysis

The EPA dossiers include data hydrolysis only if it is likely to occur. The applied estimation methods evaluate the rate of hydrolysis if relevant (hydrolysable) functional groups are present in the molecule. For few compound classes the HYDRO-programme is applied. Hydrolysis tests are not mandatory in the EC at "base set" level; for 41 of the chemicals included in this study hydrolysis data were given. Only for 6 chemicals were both measured and predicted hydrolysis data available. A comparative analysis of this end-point was therefore not carried out.

4.2.1.7. Soil Sorption

The environmental fate analysis carried out by the EPA includes in general the prediction of log K_{oc}. For the majority of the chemicals within this study log K_{oc} predictions were available. The applied estimation methods are mostly based on log P_{ow}, but they are of limited applicability. The fragment method can be applied more widely, but it also does not satisfy all requirements.

Under the sixth amendment no tests on soil sorption are required in the EC; for notifications according to the seventh amendment a screening test on adsorption/desorption will be mandatory. For this study no test results were available for comparison.

4.2.1.8. Photodegradation

The environmental fate analysis of the EPA experts includes estimates of the photolysis of the substance (direct and indirect) in water. Measured photolysis data are not required at "base set" level and are therefore in general not available. A comparative study is not possible on the data available.

4.2.2. Ecotoxicity parameters

4.2.2.1. Toxicity to aquatic organisms

For predicting aquatic toxicity approximately 300 SAR models are available to the EPA experts for various (about 100) chemical classes. The estimation methods are mostly based on log P_{ow}; only calculated values of this latter parameter are used. Expert knowledge is required for the selection of the appropriate SAR model. The selection is based on the chemical class, not on the mode of action. The EPA's SAR predictions cover both acute and chronic toxicity for aquatic organisms. Fish, daphnia, algae and, for some pesticid structures, also vascular plants are considered. For some chemical classes, if log P_{ow} is above 5 it is assumed that there are no acute toxic effects. Nevertheless, for those substances, and similarly for chemicals for which no toxic effect is predicted at the water solubility limit, chronic effects may still be substantial. The data on aquatic toxicity are used for risk assessment and assignment of "level of concern".

In the EC according to the requirements of Directive 79/831/EEC (sixth Amendment) at "base set" level, normally only acute fish and daphnia studies are conducted. Chronic effects and effects on species other than fish and daphnia, e.g. algae, are in general not addressed at this stage. The aquatic toxicity data are used for risk assessment and for the classification "dangerous for the environment".

In several cases, the data were given as $>n$, $<n$ or as NTS (Non Toxic at Saturation). LC/EC50 data given as $<n$ are difficult to interpret because in those cases, the actual LC/EC50 value can be much lower than the given limit. For this reason those data were excluded from analysis. Values given as $>n$, however, can be used because usually, the given limit will be regarded as a worst case estimate of the toxicity. The analysis includes therefore those chemicals for which exact and "higher than" ($>n$) effect concentrations are supplied; data presented as NTS are also included.

The comparative analysis is carried out applying the following criteria:

- for all values given as $>n$ the numbers are directly compared without considering the signs;
- for data pairs with both values above 100 mg/l, no differentiation is made between the numerical values: the ratio of estimated/measured value therefore is 1;
- the values are considered to be in agreement if they are within $\pm$ 1 log unit;
- for data pairs in which one value is given as NTS and the other as a numerical value, the results are assessed considering the water solubility: for a numerical value much higher than the water solubility (>100 mg/l) the SAR and experimental value are deemed to be in agreement; for effect concentrations closer to the water solubility (<100 mg/l) the two values are deemed to be inconsistent with one another (disagree).

The results of the comparative analyses are given in Table 6 (Toxicity to fish) and Table 7 (Toxicity to daphnia, the detailed analyses are given in the Annexes 9 and 10.

TABLE 6: Comparison of data on toxicity to fish

	N° of chemicals	%
Total	130	100
Agreement	107	82.3
Disagreement	23	17.7
- Overestimation	14	10.8
- Underestimation	9	6.9

TABLE 7: Comparison of data on toxicity to Daphnia

	N° of chemicals	%
Total	127	100
Agreement	90	70.9
Disagreement	37	29.1
- Overestimation	20	15.7
- Underestimation	17	13.4

Some of the differences in predicted and experimental toxicity can be attributed to nominal instead of measured concentrations, the use of solvents to enhance water solubility and to different test durations (24/48 hr for daphnia). For only 5 chemicals were measured and predicted data on algae toxicity available. In 4 cases, agreement between SAR/MPD data is observed (data: see Annex 11).

- Conclusions

Information on aquatic toxicity is used both for risk assessment and for classification purposes. Overall, SAR predictions of aquatic toxicity are quite good. For fish toxicity the predictions tend to overestimate the toxicity. For daphnia over- and underestimations occurred at about the same rate. Further effort is desirable to explain the cases where the reason for the underestimation (false negative predictions) is not evident. Nevertheless, if used with the required caution, SAR predictions can be very effective in the context of the US notification scheme.

The predictions are considered to represent a very useful future option to support the decision taking process within a stepwise risk assessment scheme for carrying out toxicity tests.

4.2.2.2. Classification "Dangerous for the Environment"

The EC scheme for classification "dangerous for the environment" is driven by toxicity, biodegradability and/or bioaccumulation potential. For certain types of substances (those which show low solubility in water) the water solubility may also be taken into account when determining the final classification.

The EC classification criteria and the resulting risk phrases (R-phrases) for the aquatic environment are as follows:

R 50: Very toxic to aquatic organisms

Acute toxicity:	96 hr LC 50 (for fish)		≤1 mg/l
	or	48 hr EC 50 (for Daphnia)	≤1 mg/l
	or	72 hr IC 50 (for algae)	≤1 mg/l

R 50: Very toxic to aquatic organisms
and
R 53: May cause long-term adverse effects in the aquatic environment

Acute toxicity:	96 hr LC 50 (for fish)		≤1 mg/l
	or	48 hr EC 50 (for Daphnia)	≤1 mg/l
	or	72 hr IC 50 (for algae)	≤1 mg/l

and the substance is not readily degradable
or the log P_{ow} ≥3.0.

R 51: Toxic to aquatic organisms
and
R 53: May cause long-term adverse effects in the aquatic environment

Acute toxicity:	96 hr LC 50 (for fish)		1 mg/l < LC 50 ≤10 mg/l
	or	48 hr EC 50 (for Daphnia)	1 mg/l < EC 50 ≤10 mg/l
	or	72 hr IC 50 (for algae)	1 mg/l < IC 50 ≤10 mg/l

and the substance is not readily degradable
or the log P_{ow} ≥3.0.

R 52: Harmful to aquatic organisms
and
R 53: May cause long-term adverse effects in the aquatic environment

Acute toxicity:	96 hr LC 50 (for fish)		10 mg/l < LC 50 ≤100 mg/l
	or	48 hr EC 50 (for Daphnia)	10 mg/l < EC 50 ≤100 mg/l
	or	72 hr IC 50 (for algae)	10 mg/l < IC 50 ≤100 mg/l

and the substance is not readily degradable.

R 53: May cause long-term adverse effects in the aquatic environment

Substances not falling under the criteria above, but which, on the basis of the available evidence concerning their persistence, potential to accumulate, and predicted or observed environmental fata

and behaviour may nevertheless present a long-term and/or delayed danger to the structure and/or functioning to the aquatic ecosystems.

E.g. poorly water soluble substances, i.e. substances with water solubility < 1 mg/l, will be covered by this criteria if: a) they are not readily degradable
b) and the log P_{ow} ≥3.0.

Further details are to be found in the complete EC classification and labelling guide which is attached as Appendix 3.

In this comparative study the EPA's quantitative predictions are used to classify the chemicals according to the EC criteria. The results are compared to those classifications based on the measured data. All 144 chemicals in the project were classified for the comparison purpose on the data available, independent of whether the data sets - both measured and predicted - were complete or not. The comparison and the results are given in Tables 8 and 9.

TABLE 8: Comparison of classification "dangerous for the environment" according to the EC scheme based on MPD vs SAR data

Classif. based on MPD data	Total	Classification based on SAR data					
		N.c.*	R53	R52/53	R51/53	R50/53	R50
Not class.	48	28	6	6	3	3	2
R53	23	2	17	-	-	4	-
R52/53	26	8	4	4	7	3	-
R51/53	34	5	3	3	14	9	-
R50/53	13	1	2	1	2	7	-
R 50	-	-	-	-	-	-	-
Total	144	44	32	14	26	26	2

* Not classified

TABLE 9: Result of the comparison of classification "dangerous for the environment"

	N° of chemicals	%
Total	144	100
Agreement	70	48.6
Disagreement	74	51.4
- Overclassification	43	29.9
- Underclassification	31	21.5

Conclusions

The overclassifications can be considered acceptable as being conservative. The agreement of 78% when including the overclassifications is encouraging, even though the underclassifications give cause for concern since potentially dangerous substances may not be recognized.

The concordance in classification of chemicals "dangerous for the environment" is in general reasonably good. However, for the purpose of classification within a legislative scheme, the use of measured data is clearly preferable.

4.2.3. Toxicological properties/health effects

4.2.3.1. Absorption

The likely extent of absorption of a chemical via skin, lungs and gastro-intestinal tract is predicted by the EPA experts on the basis of the physico-chemical properties of the chemical (particularly log P_{ow}, which is usually a predicted value, and the physical form of the chemical). The initial opinion on this basis may be modified in the light of any available test data on the chemical itself or on a closely related structural analogue. Good, moderate, poor or no absorption will be predicted for each route of exposure (dermal, inhalation and oral).

The prediction of the likely extent of absorption following exposure by a particular route will be used when taking decisions on whether the chemical may present an unreasonable risk to human health and/or on testing requirements in the USA.

Absorption is not investigated in the base-set level testing in the EC, but whether any absorption has occurred can be inferred to an extent from evidence of systemic toxicity in the acute and repeated dose studies. It is less easy to decide that absorption has not occurred - the chemical may be well absorbed and show no systemic toxicity in the particular test(s) already conducted. However, it may cause adverse effects in other test systems not yet applied. Evidence of absorption (i.e. systemic effects) may have an influence on the timing of further testing. When there is no evidence from the currently available test data, the timing of further testing may be influenced by the likelihood of absorption based on the physico-chemical properties of the chemical and/or the extent of human exposure expected.

- Conclusions

There were too few studies conducted using the inhalation route for an accurate assessment of concurrence between SAR calls for absorption from the lungs and derived absorption estimates from toxicity test results.

Based on the 136 chemicals for which dermal toxicity studies were available, it is considered that acute dermal studies are inadequate to judge dermal absorption. There were too few 28-day studies to serve as a basis for definitive judgement on dermal absorption calls.

The SAR calls for gastro-intestinal absorption were essentially in agreement with estimates based on the oral toxicity test results: when they differed it was only in degree of absorption and not, with one exception, giving a completely different assessment of whether or not a chemical was absorbed at all. For some chemicals, which were classified in the EC on the basis of their oral toxicity, the relatively low extent of absorption predicted may be of some concern. However, none of these chemicals were predicted to have "no absorption" and thus would not have been dropped from EPA evaluations.

4.2.3.2. Acute toxicity

Acute toxicity data are used to predict the potential effects in humans of a single exposure to a chemical (e.g. during maintenance work or in an accident). They are also used to help in setting dose levels for other toxicity tests.

Prediction of acute toxicity is not emphasised in the EPA evaluation of a new chemical which focuses on long-term or sub-chronic effects. For the purposes of this project, however, predictions of acute toxicity following oral administration were made. (There were too few chemicals with data from inhalation or dermal acute toxicity tests which were suitable for conducting comparisons of the two approaches to evaluation.)

The following criteria were used to rank chemicals on the basis of their oral LD50 values, and so provide a means of comparing the predicted toxicity with that observed in the tests:

Oral LD50 (mg/kg)	Toxicity
>2000	Low (L)
>1000 <2000	Low-Medium (L-M)
> 500 <1000	Medium (M)
> 50 < 500	Medium-High (M-H)
< 50	High (H)

These criteria give more categories of acute toxicity than are conferred by the EC classification system (below), but the same criterion (LD50 >2000 mg/kg) is used to differentiate chemicals of low concern with regard to acute oral toxicity from those of some level of concern.

Oral LD50 (mg/kg)	EC classification
>2000	Not classified
> 200 <2000	Harmful
> 25 < 200	Toxic
< 25	Very toxic

Acute oral toxicity tests had been conducted on 142 chemicals (two chemicals had not been tested: chemicals 4 and 107 are corrosive and react violently with water). A prediction of acute oral toxicity had been made for all of the 142 chemicals which had been tested, plus the two which had not.

There were 21 chemicals for which the toxicity indicated by the test data differed from that predicted (15%). Twenty of these were found to have greater acute toxicity than had been predicted, but for fourteen of these there was overlap between the predicted and observed toxicity categories, (see Table 10). One chemical had lower toxicity than had been predicted (number 124).

Twenty-one chemicals had been classified in the EC on the basis of their acute oral toxicity: twenty of them are included in Table 10 and were predicted to have lower toxicity than was observed, though for 14 there was an overlap between predicted and observed toxicity categories. However, 18 of the classified chemicals (12%) were predicted to be of "low" acute oral toxicity, and thus would apparently be considered of low concern with regard to this end-point (false negatives). The classified chemical which is not in Table 10 (number 281) was predicted, by analogy to data in the EPA confidential data base, to have "medium" acute toxicity and this was observed (LD50 = 850 mg/kg). Details of the oral toxicity predictions and test results are given for all chemicals in the project in Annex 12.

- Conclusions

Using arbitrary criteria to compare LD50 values with descriptions of predicted acute oral toxicity, there was a tendency to under-prediction of the level of toxicity for chemicals which, when tested, were shown to have significant acute oral toxicity. However, the majority of the chemicals were correctly predicted to be of low concern with regard to acute oral toxicity.

Predicted toxicity for 18 (12%) of the classified chemicals was "low", indicating that one-to-one substitution of predictive methods for testing would result in chemicals being missed which are, in fact, of some potential concern because of acute toxicity. It should be noted that two of these chemicals had been classified as "Toxic if swallowed" (numbers 307 and 330).

In most cases there were overlaps between the predicted and the observed toxicity for the classified chemicals, and between the toxicity predicted for the classified chemicals and those not classified. Hence, the predictive methods could not readily be used to classify chemicals within the context of a scheme using pre-defined criteria.

Thus, this comparative study shows that the predictive methods can be used to identify correctly the >80% of a batch of 142 heterogeneous new chemicals which are of low acute toxicity. However, it is of concern that some 12% of this set of chemicals did have an appreciable level of acute oral toxicity which was not predicted (false negatives). Because of this outcome, if assessment of acute toxicity is an important consideration in a given evaluation scheme, the submission of test data will be needed to assess this end-point adequately. This is especially so in instances where a quantitative assessment of acute toxicity is needed.

TABLE 10: Differences between SAR evaluations and acute oral toxicity test data

Chemical	LD50	Label[1]	MPD tox[2]	SAR tox[2]
47	1800	R22	L-M	L
49	>200 <2000	R22	L-M	L
54	1984	R22	L-M	L
124	2300	-	L	M
156	1800M 1960F	R22	L-M	L
197	612	R22	M	L
219	1670	R22	L-M	L
241	585	R22	M	L
242	520	R22	M	L
300	1011	R22	L-M	L
307	88	R25	M-H	L
312	1774	R22	L-M	L
330	104	R25	M-H	L
340	1750	R22	L-M	L
360	>1000 <2000	R22	L-M	L
370	1400	R22	L-M	L
413	1200	R22	L-M	L
425	1650	R22	L-M	L
436	899	R22	M	L
441	450	R22	M-H	M
443	320	R22	M-H	M

[1] See Appendix 3 for list of "R phrases".
[2] See abbreviations above.

4.2.3.3. Irritation

Knowledge of the potential for skin, eye and respiratory irritation is important when evaluating safe handling practices for chemicals. Skin and eye irritation test data are used to predict the likelihood that exposure of human skin or eyes to a chemical will result in adverse effects (corrosion or irritation). An indication of the duration/reversibility of effects is also usually obtained.

There is not a test method for respiratory irritation in either the EC or the OECD set of accepted test methods for the toxicity testing of chemicals.

Prediction of irritation is not usually part of the routine evaluation of new chemicals in the US, but predictions were made for the purposes of this project, although EPA did not attempt to characterise the degree of irritation.

4.2.3.3.i Skin irritation

The criteria used for conducting the comparisons were to compute "primary irritation scores" from the test data, by taking the average of the total erythema and oedema scores for both the 24 and 72 hour readings:

Primary irritation index	Irritant category
2 or less	Mild/nil (low)
>2 to 5	Moderate
>6	Severe

The category "corrosive" was also used.

In addition, chemicals were also considered according to whether they had been classified as "Corrosive" or "Irritating to skin" in the EC.

Of the total of 144 chemicals in the project, there were 140 on which skin irritation tests had been conducted. All 144 chemicals had been considered when predicting the potential for skin irritation as a consequence of dermal exposure to the chemicals.

Correct predictions of low concern for skin irritation were made for 104 of the 122 chemicals (including the untested polymer, chemical number 267) for which the test results indicated little or no irritancy (83% of the 122 chemicals; 73% of the total number of chemicals in the project). There were 18 chemicals which were predicted to be irritating to skin, but were found not to be irritant in the test conducted, i.e. false positives.

The test results (or physico-chemical characteristics of three chemicals: numbers 4, 107 and 194) showed that 22 chemicals either were, or could be expected to be, at least moderate skin irritants. Twelve of these had been classified as "Corrosive" in the EC, and six as "Irritating to skin". The outcome of the comparisons for the classified chemicals is shown in Table 11. Ten of these were identified by EPA as being skin irritants, while for the remaining 8, EPA did not identify a concern for skin irritation (false negatives). The group of false negatives included six corrosive chemicals.

TABLE 11: Comparison of predicted skin irritancy with that observed

Chemical	Label[1]	MPD result[2]	SAR result	Agreement[3]
4	R35	Corrosive[4]	Acute	Yes
49	R34	Corrosive	Irritant	Yes
53	R38	Mod - Sev	Irritant	Yes
107	R35	Corrosive[4]	Acute	Yes
118	R34	Corrosive	No comment	False -ve
182	R34	Corrosive	No comment	False -ve
192	R34	Corrosive	No comment	False -ve
194	R34	Corrosive[4]	No comment	False -ve
222	R38	Moderate	Irritant	Yes
235	R34	Corrosive	No comment	False -ve
237	R38	Low - Mod	Irritant	Yes
278	R38	Moderate	Irritant	Yes
370	R34	Corrosive	Irritant	Yes
373	R38	Moderate	No comment	False -ve
425	R34	Corrosive	Irritant	Yes
436	R34	Corrosive	No comment	False -ve
437	R38	Mod - Sev	Irritant	Yes
443	R34	Corrosive	No comment	False -ve

[1] See Appendix 3 for list of "R phrases".
[2] According to the criteria above, using primary irritation score.
[3] Predicted relative to test-derived level of skin irritancy.
[4] Chemicals not tested: EC assumed corrosivity based on physico-chemical properties.

The overall results for the comparison of SAR calls and MPD data for skin irritation are summarised in Table 12. In this Table, MPD positive includes the three chemicals considered corrosive in the EC on the basis of physico-chemical properties (chemicals 4, 107 and 194); and SAR negative includes the two chemicals for which the prediction was "uncertain". Details of the data on skin irritation for all chemicals are to be found in Annex 13.

TABLE 12: Overall results for skin irritation

	SAR Positive	SAR Negative
MPD Positive	14 (10%)	8 (5.5%)
MPD Negative	18 (12.5%)	104 (72%)

- Conclusions - skin irritation

Incorrect predictions were obtained for 18% of the chemicals: 12.5% were false positives and 5.5% were false negatives. The predictive methods used are not adequate for classification of chemicals using a system based on severity of response and thus the test cannot be replaced on a one-to-one basis by the predictive approach when knowledge of the potential for skin irritation/corrosion is needed.

4.2.3.3.ii Eye irritation

The criteria used to compare the test data with the SAR call for eye irritation could not be made on a severity index as the SAR evaluations did not usually include this index. From the test data summaries, a chemical was considered to produce significant eye irritation if redness, swelling or corneal opacity persisted beyond seven days or if effects were not reversible by 21 days or corrosion was reported. Eye testing was not conducted on chemicals with predictable corrosivity because of their physico-chemical characteristics or, for some chemicals (see Table 13), if corrosive effects had been recorded in a previously conducted skin test.

Classification according to the EC system (for which the criteria are a combination of scores and duration of effects), on the basis of the results of the eye irritation studies, was obviously also considered as indicating that the classified chemicals were eye irritants.

Of the total of 144 chemicals in the project, there were 140 on which eye irritation tests had been conducted, three were predicted to be corrosive and one (number 267) could not be tested for technical reasons. All 144 chemicals had been considered when predicting the potential for eye irritation as a consequence of ocular exposure to the chemicals.

On the basis of the test results, 105 chemicals were considered to be of low concern for eye irritation, as was chemical 267, which had not been tested. Correct predictions of low concern were made for 87 of these (83% of the "negative " chemicals, 60% of the total set of chemicals). The other 18 were predicted by the EPA to be irritant i.e. they were false positives.

The 38 remaining chemicals were either corrosive (12 chemicals), or irritant according to the criteria given above. The outcome of the comparisons between the predicted and test results for the classified chemicals is given in Table 13, the detailed analysis for all chemicals in the project is given in Annex 13.

TABLE 13: Comparison of predicted eye irritancy with that observed

Chemical	Label[1]	MPD result[2]	SAR result	Agreement[3]
4	R35	Corrosive[4]	Acute	Yes
47	R41	Severe	Uncertain	False -ve
49	R34	Corrosive	Irritant	Low
87	R41	Severe	No comment	False -ve
107	R35	Corrosive[4]	Acute	Yes
118	R34	Corrosive[4]	No comment	False -ve
124	R36	Irritant	Irritant	Yes
151	R36	Irritant	Irritant	Yes
170	R41	Severe	Irritant	Yes
182	R34	Corrosive	Irritant	Low
192	R34	Corrosive	No comment	False -ve
194	R34	Corrosive[4]	No comment	False -ve
197	R41	Severe	No comment	False -ve
222	R36	Irritant	Irritant	Yes
235	R34	Corrosive[4]	No comment	False -ve
237	R36	Irritant	Irritant	Yes
256	R36	Irritant	Irritant	Yes
263	R36	Irritant	Irritant	Yes
270	R36	Irritant	No comment	False -ve
281	R36	Irritant	Irritant	Yes
370	R34	Corrosive[4]	Irritant	Low
425	R34	Corrosive[4]	Irritant	Low

TABLE 13 - continued

Chemical	Label[1]	MPD result[2]	SAR result	Agreement[3]
436	R34	Corrosive[4]	No comment	False -ve
441	R41	Severe	Irritant	Yes
442	R41	Severe	Irritant	Yes
443	R34	Corrosive[4]	No comment	False -ve

[1] See Appendix 3 for list of "R phrases"

[2] According to the criteria given in the text

[3] Predicted relative to test-derived result

[4] Chemicals not tested: corrosivity assumed based on physico-chemical properties or results of skin irritation study

From the comparisons given in Table 13, it can be seen that, for the 26 classified chemicals, 16 were correctly predicted to be eye irritants and 10 were incorrectly assessed (false negatives).

The overall results for the comparison of the SAR calls and the MPD test results are summarised in Table 14.

TABLE 14: Overall results for eye irritation

	SAR Positive	SAR Negative
MPD Positive	26 (18%)	13 (9%)
MPD Negative	18 (13%)	87 (60%)

Conclusions - eye irritation

Incorrect predictions were made for 22% of the chemicals (9% were false negatives, 13% false positives). As with skin irritation, predictive methods are not adequate for classification of chemicals with regard to severity of the response and thus cannot replace test results on a one-to-one basis.

4.2.3.3.iii Respiratory irritation

New chemicals are not tested for respiratory irritation in the EC, but the potential for respiratory respiration had been considered by the EPA predictors.

Predictions of potential respiratory or mucous membrane irritation had been made for 9 (6%) of the chemicals in this study.

- General conclusions

The majority of this group of new chemicals was of low concern for skin (85%) and eye (74%) irritancy. Thus, the extent to which an assessment can be made of the power of the predictive methods to discriminate between chemicals on the basis of their skin or eye irritation potential is limited.

The majority (>80%) of the low concern chemicals were predicted correctly and 18% were over-predicted for either or both of skin and eye irritancy. The latter observation means that for these substances, the risk assessment would err on the side of caution but would lead to "over-labelling" if the predictive methods replaced the tests.

The incidence of false negatives and the limitations in assessing severity of response are of some concern and indicate that replacement of testing with prediction cannot yet be recommended with confidence.

Respiratory irritation is an important end-point which is not investigated in the MPD. It would be prudent to take note of chemicals predicted to be respiratory irritants.

4.2.3.4. Sensitisation

Knowledge of the sensitising potential of chemicals is important when evaluating safe handling practices.

Prediction of sensitisation is not usually part of the routine evaluation of a new chemical in the US, but it was considered for this project.

In the EC, chemicals are tested for their skin sensitising potential. There is not an internationally recognised test method for respiratory sensitisation. Classification of notified new chemicals as skin sensitisers in the EC is based on the proportion of animals showing a positive response in a particular test. In the EC, chemicals may be classified as respiratory sensitisers if they show close structural similarity to known chemical respiratory sensitisers.

Skin sensitisation tests, mostly maximisation tests, were conducted on 137 of the chemicals in the project. Twenty eight chemicals were classified as skin sensitisers (including one of those which had not been tested). A further 18 induced some positive responses but the number of animals responding was below the threshold for classification in the EC.

Seventeen chemicals were predicted to be sensitisers; four of these were predicted to be respiratory sensitisers and one was predicted to be a photosensitiser. Two were predicted not to be sensitisers. For most of the chemicals there was no comment on skin sensitisation - this is equivalent to considering the chemical of low concern/negative for this end-point.

For 108 chemicals (75% of the whole set in the project), both the test results and the predictions indicated low concern for skin sensitisation.

The results of the comparisons of the test data and the predictions are given in Table 15 for the 28 chemicals classified as skin sensitisers in the EC.

TABLE 15: Comparison of results for chemicals classified as skin sensitisers

Chemical	SAR	Result and comments
47	-	False negative
76	+	Agree
96	-	False negative
118	-	False negative
133	-	False negative
173	+	Agree
194	-	False negative NB: chemical not tested
196	+	Agree
197	-	False negative
200	-	False negative
222	+	Agree Chemical also classified and predicted as a respiratory sensitiser
235	-	False negative
256	+	Agree
271	-	False negative
275	-	False negative

TABLE 15 - continued

Chemical	SAR	Result and comments
330	+	Agree
341	+	Agree Chemical also classified and predicted as a respiratory sensitiser
344	-	False negative
348	-	False negative
376	+	Agree
393	-	False negative
401	-	False negative
413	-	False negative
416	-	False negative
437	-	False negative
442	-	False negative
444	-	False negative

Five other chemicals were predicted by the US to be skin sensitisers: one did not have adequate test data (240); two did induce some positive responses in the tests conducted (253, 312) and two were apparently false positive predictions (340, 364).

Two other chemicals were predicted to be potential respiratory sensitisers (69, 101).

For the set of comparable skin sensitisation data (140 chemicals) the comparisons in Table 16 can be made.

TABLE 16: Overall results for skin sensitisation

	SAR Positive	SAR Negative
MPD Positive	9 (6.5%)	19 (13.5%)
MPD Negative	4*(3%)	108 (77%)

* includes two substances for which positive responses, below the threshold for classification, where observed in the tests

Conclusions

The incidence of false negatives precludes use of the predictive methods to replace the tests on a one-to-one basis or to classify chemicals for their skin sensitisation potential. However, the concurrence of positive predictions with positive test results needs to be further assessed with a larger set of chemicals as confidence in the ability to predict positives could perhaps replace testing of chemicals predicted to be skin sensitisers.

For respiratory sensitisation, reliance is currently placed on predictive methods, based on structure, to classify new chemicals in the EC, and the unclassified substances predicted, in this project, to be potential respiratory sensitisers should be re-evaluated in the EC with regard to classification.

It is not possible to comment on the single prediction of potential photosensitisation.

4.2.3.5. Repeated dose toxicity

Repeated dose toxicity covers the adverse effects which may arise in humans exposed to a chemical at frequent, regular intervals over a prolonged period of time, for example at their daily work. To facilitate evaluation of safe handling practices for chemicals, it is important to have knowledge of the potential systemic effects which may occur on repeated exposure.

In the EC, general effects on the whole animal and effects on tissues, organs and/or systems are investigated. Special effects (e.g. neurotoxicity, reproductive toxicity, carcinogenicity) are investigated in specific tests, but indications of potential reproductive toxicity, neurotoxicity or immunotoxicity may be detected in repeated dose toxicity studies.

For most of the chemicals in this project only 28-day, and/or occasionally 90-day, study results were available. In the EC study summaries used for this project, dose levels used, a description of toxic signs, including clinical chemistry and haematology, gross and microscopic changes in a selected set of tissues/organs, and NOEL, NOAEL, LOEL and LOAEL (no/low observed effect/adverse effect level) values are usually included or can be deduced. In general, only effects of biological significance are included and species specific effects (e.g. peroxisome proliferation and, in the more recent summaries, male rat specific light hydrocarbon nephropathy) are not. Chemicals are classified for repeated dose toxicity in the EC on the basis of adverse effects (of biological/human significance) occurring at or below dose levels specified according to the route of exposure and the duration of the study.

Predictions of repeated dose toxicity are particularly important in the US EPA evaluation process, with identification of potentially toxic chemicals as the goal. Efforts are also made to assess potential target tissue/organ/system.

Test data were not available for seven chemicals (3 corrosive chemicals, 2 polymers, 1 organoclay and one chemical not tested in the light of test data available for another notified chemical, of very similar structure). Two chemicals had been tested in 28-day inhalation studies and eight in dermal 28-day studies. For one of the latter group, a 90-day study had also been conducted. The remaining 127 chemicals had been tested using 28-day oral toxicity studies and three also had results available from 90-day studies.

Eight chemicals had been classified in the EC on the basis of their repeated dose toxicity.

The comparison of repeated dose toxicity test results with predicted toxicity was the most difficult to do as interpretation of observed effects in terms of severity and significance is a matter of professional judgement. The factors considered in the evaluation were the perceived seriousness of the toxic effect, the number of organ-specific parameters affected, with microscopic pathology given the heaviest weight, multiplicity of target organs, the toxic effect(s) at the LOAEL, the numerical value of the NOAEL, dose-related effects and the spacing of the dose levels used.

The systemic toxicity data from the test results were scored as high, moderate or low using the following general criteria (sometimes modified according to professional judgement):

Concern level	Criteria
Low (L)	No systemic toxicity (NOAEL 1 g/kg/day or more); only minor clinical signs of toxicity; liver and/or kidney weight increase or clinical chemistry changes; LOAEL > 500 mg/kg/day.
Moderate (M)	Organ pathology (gross and/or microscopic) with LOAEL 500 mg/kg/day or less; clinical chemistry changes and organ weight changes at < 500 mg/kg/day; NOAEL < 100 mg/kg/day.
High (H)	Death, organ pathology (microscopic) at LOAEL 100 mg/kg/day or less; multiple organ toxicity; NOAEL < 10 mg/kg/day.

"Split-levels" (L-M; M-H) were adjustments for specific multiple organ toxicity, borderline effect levels and professional judgement.

The outcome of the comparisons of repeated dose toxicity on the basis of concern level is summarised in Table 17.

TABLE 17: Matrix analysis of systemic toxicity concern levels

SAR	L	L-M	M	M-H	H
MPD					
L	62	10	5	0	0
L-M	23	11	2	0	0
M	11	1	5	1	1
M-H	3	1	2	3*	0
H	1	0	0	0	1*

* 1 chemical in each of these groups was corrosive and predicted to have acute effects

One chemical (337) is not included in the matrix. It was M-H according to the test results, but there was no prediction of repeated toxicity.

Sixty-two chemicals (43%) were considered of low concern both following testing and by the predictive methods.

Twenty chemicals (14%) with greater than "low" concern were predicted to have the same level of concern as was deduced from the test data using the criteria given above. This group included the two corrosive chemicals which were predicted to have "acute" effects (numbers 4 and 107) and chemical 292 for which data were available from the product literature.

The concern level was under-predicted for 42 chemicals (29%) though for 27 chemicals there were overlapping concern levels from the test and predicted results; and 23 of these predicted to be of low concern were only low-moderate from test results. For the other 15 the concern level predicted was at least one whole level lower than that deduced from the test data. Six of this sub-set of 15 were chemicals classified in the EC on the basis of repeated dose toxicity.

Toxicity concern was apparently over-predicted for 19 chemicals. However, the extent of repeated dose toxicity testing of these chemicals was limited to 28-day studies (18 oral studies, 1 dermal). It will be of interest, if/when 90-day, or longer, study data become available, to re-compare the predicted toxicity with that found on testing.

Overall, the correct level of concern (according to the criteria given above) was predicted for 57% of the chemicals, but was under-predicted for 29%. Toxicity was apparently over-predicted for 13% of the chemicals.

Details of the organ toxicity predictions and test results are given for all the chemicals in the project in Annex 14.

Conclusions

Just over half (57%) of this group of 143 heterogeneous chemicals were correctly predicted to be either of low concern (43% of the total) or to have the same level of concern (14% of total) in relation to repeated dose systemic toxicity. The concern level was apparently over-predicted for a further 13%, but if/when longer-term studies are conducted the predicted effects may be induced.

Under-prediction of the level of concern on the basis of repeated dose toxicity was noted for 42 chemicals (29% of the total), although for 23 of these, the test data indicated only low-moderate concern and EPA predicted low concern. For 15 chemicals, there was at least one whole "level of concern" difference, and six of the eight classified chemicals were in this group.

On the basis of these comparisons, although for 74% of the chemicals in this study, correct or near-correct predictions of concern level were made, it is not considered possible to consider the predictive methods as an adequate substitute for conducting repeated dose toxicity testing of a random/heterogeneous group of chemicals because of under-prediction of toxicity. As classification of a chemical as dangerous following repeated exposure depends not only on the effects seen, but also on the doses at which they occur, the predictive methods for repeated dose toxicity would not provide a firm basis for classification.

4.2.3.6 Mutagenicity

Chemicals which increase the incidence of mutations in the cells of exposed humans may thereby increase the incidence of cancer (from mutations in somatic cells) or genetic defects in the offspring (from mutations in germ cells). It is generally thought prudent to assume that there is no threshold exposure level, below which exposure would give rise to only low concern, for chemical mutagens. Thus, chemicals identified as mutagens are subject to stringent controls so that human exposure is minimised.

Because of the serious and irreversible effects which may occur in humans exposed to chemical mutagens, testing for mutagenicity usually employs a number of tests, in vitro and in vivo, which are conducted either as a battery or (as in the EC) in series. In the EC, all notified chemicals must, if it is technically possible, be tested in a bacteriological test for gene mutation and in a test in mammalian cells for chromosomal effects at the "base-set" level of supply. The latter test may be either an in vitro test or a test conducted in vivo. Maximised conditions are used, though short of conditions likely to cause artefactual positive results; and in vitro tests are conducted both with and without exogenous metabolic activation. Further testing is conducted to investigate in more detail positive test results, as necessary, and/or as supply tonnages reach the trigger levels. Classification of chemicals on the basis of mutagenicity is done according to criteria defined in Annex VI to the dangerous substances Directive. Chemicals are not usually classified unless there is evidence of mutagenicity from tests conducted in vivo, so positive in vitro test data will trigger the need for testing in vivo.

The EPA predictions for mutagenicity, based on e.g. chemical class, analogue data, likely metabolites, alkylating potential, represent an overall for mutagenic potential. EPA also considers available data concerning mutagenicity test systems and their sensitivity towards different classes of chemicals. Thus, the criteria for comparing the predicted with the test results involved more than a simple comparison of EPA predictions with the test data. In addition, the test results for a few (6, 4%) chemicals with borderline responses were not always interpreted in the same way by the EPA and EC experts.

Tests had not been conducted on five of the 144 chemicals in the project - 3 for technical reasons (chemicals 4 and 107 were corrosive and chemicals 267 was an insoluble polymer) and for the other two (chemicals 194 and 445) data from analogues were considered acceptable. Predictions had been made for the first three (all were "low concern" for mutagenicity) but there were no test data to compare them with. Thus, there were 141 data pairs for comparison. All of the 139 chemicals tested had Ames test data and all had at least a result from one other study. The in vivo micronucleus test occurred most frequently as the second study, and the in vitro chromosome aberration test was next most common. Tests in E coli (always alongside the Ames test when the E coli test had been conducted); in vivo chromosome aberration, nuclear anomaly and sister chromatid exchange (SCE) tests and in vitro mammalian cell gene mutation assays, unscheduled DNA synthesis, and SCE tests also occurred in this set of tests. Interestingly, for no chemical was there more than one positive test.

One hundred and twenty chemicals gave negative results in both a bacteriological (Ames) test and a non-bacteriological test. Some of these chemicals also had negative results from gene mutation tests in E coli and/or from other non-bacteriological tests. Two chemicals were assumed by analogy to structurally similar chemicals to be negative and were not tested. Thus, following testing, 122 chemicals (85% of the chemicals in the project) were considered negative. SAR predictions of low concern for mutagenicity were made for 107 chemicals in this group (88% of the MPD "negatives").

Depending on how the analysis is done "false positive" predictions were made for 14 (10% of total) or 2 (1.4%) chemicals. A direct reading of the MPD results would lead one to conclude that there were 14 false positive predictions. However, EPA considers that positive results would be produced if tests were performed using assay systems other than those used already to test the affected

chemicals. The EPA conclusions are based on the existence of data on analogues (chemical or mechanistic) indicating positive results in certain test systems. It will be of interest (and potential importance) to see whether the predictions of positive mutagenicity are fulfilled if further test data become available.

Six chemicals (4% of total) with positive test data were predicted "low" (false negatives) because of absence of known positive data in analogues.

The test results (including, where appropriate, an indication of weak positive results), EPA predictions and results of comparison are given in Annex 15 for all of the chemicals in the project.

- Conclusions

A high proportion of the chemicals in this project were negative for mutagenicity and a high proportion of these were correctly identified by the EPA.

Although the number of test-positive chemicals was small, it is also of concern that six of them were called low. The observation that 123 of 142 data pairs (87%) were apparently correctly predicted thus has to be seen in the light of the above comment. For this reason it would not be prudent at this time to replace mutagenicity testing of new chemicals in the EC with the predictive methods used in the US for PMN chemicals.

As the EC classification system for mutagenicity, as applied to notified new chemicals, depends essentially on testing in vivo to investigate whether effects observed in vitro are expressed in vivo, the predictive methods used here, which do not make this distinction, could not be used for classification in the EC.

4.2.3.7. Other effects

A number of effects were considered using the predictive methods which had not yet been investigated in the EC testing programme for the chemicals in this project i.e. reproductive and developmental toxicity, neurotoxicity and oncogenicity. For some chemicals, indications of some of these effects (e.g. clinical signs of neurotoxicity; changes affecting the reproductive organs) may be reported for the acute or repeated dose tests. Such reports were made for some chemicals in this project: five chemicals had significant indications of potential reproductive toxicity (76, 151, 186, 200 and 292) and reproductive toxicity was predicted for chemicals 200 and 292 but not for the others (developmental toxicity was predicted for chemical 76). Signs of neurotoxicity were seen with six chemicals (54, 268, 340, 342, 431 and 434) and neurotoxicity was predicted for two of these (54 and 340).

Adverse effects on reproduction and/or development were predicted by EPA for 51 chemicals (35%); 27 chemicals were predicted to be neurotoxic (19%) and 33 (23%) to be oncogenic. This is of particular concern as these potential effects are not specifically investigated in the initial testing of new chemicals in the EC.

The health concerns for which the MPD data set does not provide data were analysed for number of chemicals for which such concerns were expressed and the frequency of occurrence. Of the 144 chemicals, 66 (44%) had concerns that addressed health effects outside the scope of the MPD data set. The breakdown by effect and frequency of occurrence is presented in Table 18.

TABLE 18: Health concerns not addressed by the MPD data set

Concern	Number of chemicals	% of Total chemicals
Oncogenicity	33	23
Developmental toxicity	46	32
Reproductive toxicity	13	9
Neurotoxicity	21	15
Immunotoxicity	2	-
Photosensitisation	1	-
Lung	1	-
Respiratory sensitisation	1	-

This table indicates that potential adverse effects beyond those in the MPD were identified for a substantial number of the chemicals, which implies that hazards and possibly risks may be underestimated if these effects are not considered. There may be a need for early focused testing in at least some of these cases.

5. Overall conclusions

5.1. Conclusions: US perspective

5.1.1. Introduction/Overview

The purposes of the study were to compare the results obtained in assessing a series of European Community (EC) new chemicals using two methods - the US SAR-based (Structure Activity Relationships) approach and the EC's testing-based approach using the Minimum Pre-market Data (MPD)- and to estimate the extent to which the US hazard[1] conclusions on new chemicals might change given a "base set" of test data. The study would also provide insights into the strengths and weaknesses of specific SAR approaches and allow EPA to judge how well SAR works in other areas of application, e.g., priority setting for existing chemicals and testing.

The results of the study, as expected, were quite useful in judging many of the strengths and weaknesses of the US approach, as well as determining the utility of MPD-type data in improving US assessment capabilities. It must be pointed out, however, that as useful as the study was, there are some limitations that must be considered in the overall evaluation of the exercise. These limitations include: the small data set available, the end-points used for comparison were limited to the tests included in the MPD data set, different approaches to ascertaining certain parameters, and indirect measurement in some MPD data sets of one or more physical/chemical properties (i.e. extrapolation) which may or may not give a "true" result. These limitations are discussed in more detail in the following sections. However, taking into account these limitations, the MPD/SAR exercise served to confirm that the SAR approach to screening new chemicals[2] is useful and effective in identifying chemicals that may be toxic and in need of further scrutiny for US regulatory purposes. However, the SAR approach appears to have limitations in predicting physical/chemical properties under some circumstances and in predicting the exact type and level of toxicity of the chemical, especially with regard to general systemic (health) effects.

5.1.2. Results

The end-points that were assessed have been divided into four categories (physical/chemical properties, biodegradability, health effects, and ecotoxicity) for discussion purposes and appear below.

5.1.2.1. Physico-chemical properties

The physical/chemical properties routinely predicted by the SAT are: log P_{ow}, boiling point/melting point, water solubility, vapour pressure, Henry's Law constant as well as the soil sorption coefficient and the bioconcentration factor. The MPD data set contains either measured or calculated values for log P_{ow}, boiling point/melting point, water solubility, vapour pressure, and Henry's Law constant. Of these properties, there were sufficient data pairs for meaningful comparison of log P_{ow}, vapour pressure, and water solubility.

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[1]This study examined hazard (or toxicity) predictions and did not examine exposure or risk issues, other than to consider predictions of environmental fate.

[2]In the US scheme, PMN chemicals are initially reviewed by EPA's Structure Activity Team (SAT) which "screens" the chemicals to assess their fate and effects. For cases which are determined to present potentially significant risk concerns, a more detailed assessment is prepared. The present study compared the results of SAT (screening) assessments with the results of the MPD testing.

For log P_{ow} comparisons of the 144 chemicals, there were 35 for which either SAR and/or MPD data were missing, additionally, a number of the MPD values were calculated or estimated which allowed for a comparison of estimation methods, but did not provide an opportunity to compare the US estimated values with actual measured values. Applying a US/EC agreed upon standard of $\pm$ 1 order of magnitude for "good agreement," the overall agreement between the US estimates and the EC measured values was around 60%. In analysing the 40% which were in disagreement, it became apparent that the estimation techniques for log P_{ow} were of limited value with certain classes of chemicals (e.g., classes where all the molecular fragment constants have not been measured, ionic compounds, organometallics, inorganics, and classes/compounds which are readily hydrolysed). For those classes where the estimation techniques are appropriate, the agreement was acceptable and predictive approaches were judged to provide a useful alternative to experimentally determining log P_{ow}. For chemicals where models are not appropriate, experimental determination of log P_{ow} is the preferred method.

Vapour pressure comparisons presented a number of analytical problems. In the US PMN program vapour pressures below 10^{-3} torr are routinely considered "negligible" and not of concern for either worker/consumer exposure or volatilization from the pure state. Thus estimated values of less than 10^{-3} torr are in general not determined. The EC, however, considers vapour pressures relevant to 10^{-6} torr and thus requires values to be provided. In order to adjust for the differing requirements, a set of rules was generated and agreed to by the US and EC. Additionally, the vapour pressure for the EC chemicals was measured on the substance "as marketed" in the EC (i.e., a mixture or formulation, in many cases), whereas the US estimate was made for the pure chemical. The results of the analysis showed that 63% of the US estimated values were in agreement ($\pm$1 log unit) with the measured EC values. Of the 37% (42 chemicals) of the comparisons that were in disagreement, the disagreement for 30 of the chemicals can be accounted for by the following reasons:

the "measured" vapour pressure value was extrapolated from a value measured at a higher temperature which tends to overestimate the true actual atmospheric vapour pressure;

the pre-market substance tested contained a volatile solvent and/or impurities;

the substance decomposed during the measurement procedure;

the measured value reflected water which was being driven off by the measurement procedure;

vapour pressure was the lowest value measured and thus represents the upper limit rather that an actual value.

The best agreement was observed between the PCNOMO estimates and the measured values. Overall, however, vapour pressure estimates were judged to have marginal acceptability since the values were both over- and underestimated by the US. As was stated previously, vapour pressure contributes to the exposure portion of the risk assessment for new chemicals and over/under estimation can result in an over/under estimation of the exposure associated with a chemical and thus contribute to an over/under estimation of the risks. Thus incorrectly estimating vapour pressure may unnecessarily put the worker/consumer at risk or burden the manufacturer with unnecessary constraints depending upon the direction of the estimation error. Vapour pressure is a relatively inexpensive parameter to measure, and as such, it may be more cost effective and less risky/burdensome to obtain experimental data to confirm the estimated value in cases where vapour pressure is an important contributor to the risk projection.

Water solubility comparisons presented some similar problems to the vapour pressure comparisons. In the US PMN program water solubilities below 1 mg/l are not routinely estimated, because reasonably accurate estimation of extremely low water solubilities is difficult. On the other hand, the

EC data measure water solubilities of < 0.1 mg/l in many cases. In addition the EC measured value is not necessarily done on the pure chemical but many times on the substance "as marketed," whereas the US estimated value is for the pure chemical. The results of the analysis showed that 68% of the US estimated values were in agreement (± 1 log unit) with the measured EC values. Of the 32% of the comparisons (43 chemicals) that were in disagreement, the disagreement for 26 of the chemicals can be accounted for by the following reasons:

the "measured" value was not actually measured but reported as a lower limit of detection or the lowest value measured;

the pre-market substance tested contained a solvent and/or impurities which complicated interpretation of water solubility values;

the measured value was measured spectrophotometrically;

the substance decomposed or reacted with the water during the measurement procedure.

Overall the water solubility estimates were judged to have marginal acceptability since the values were both over- and under-estimated by the US. Water solubility contributes to the hazard and exposure portions of the risk assessment for new chemicals and over/under estimation can result in an over/under estimation of the hazard/exposure associated with a chemical and thus contribute to an over/under estimation of the risks. Thus incorrectly estimating water solubility may put the worker/consumer unnecessarily at risk or burden the manufacturer with unnecessary constraints depending upon the direction of the estimation error. Water solubility is a relatively inexpensive parameter to measure, and as such, it may be more cost effective and less risky/burdensome to obtain experimental data to confirm the estimated value in cases where the water solubility is an important contributor to the risk projection.

5.1.2.2. Biodegradability

Comparison of the US and EC biodegradability data was difficult due to the fundamental incompatibility of the evaluation approaches used for assessing biodegradability in the US versus the EC. The US estimates biodegradability in terms of "days, weeks, or months" which refer to the approximate amount of time (not half-life) required for complete primary and ultimate biodegradation of the chemical in aquatic environments. In contrast, the EC requires a laboratory test which evaluates the "ready" biodegradability of chemicals. Thus, while chemicals that degrade easily in the EC testing scheme would most likely be easily degraded in the environment, it is not necessarily true that chemicals not degraded in the EC tests would not be degraded under environmental conditions which is what the US approach attempts to predict. For the purposes of this exercise, chemicals that did not pass the EC test, i.e. did not degrade under conditions of the test were considered to correspond to the descriptors "weeks or longer" and ones that passed, i.e., degraded, were considered to correspond to the descriptors "days," and "days to weeks" in the US scheme. Using these criteria, there was a 93% agreement between the US predictions and the EC test results.

The US scheme for predicting biodegradability aims for a realistic assessment of the ultimate fate of a chemical under environmental conditions. In contrast, the EC testing scheme is designed to determine ready biodegradability under precise laboratory conditions. While the EC scheme may provide more quantitative results, it can be argued that the modelling by the US represents a more realistic estimate albeit qualitative. Biodegradability testing under conditions that duplicate actual environmental conditions may not be feasible either from a scientific or a cost perspective. Although the MPD/SAR analysis has significant uncertainty due to the basic differences between the two approaches, the present US modelling scheme appears to be reasonably effective in predicting

biodegradability that is consistent with experimentally derived results. However, given the uncertainty in the analysis, in the instances for which fate is a major contributor to the overall risk projection, or for classes of chemicals where there is insufficient data for modelling, it is advisable to confirm the prediction with appropriate testing.

5.1.2.3. Health effects

Although the EC requires that a base set of toxicity data be submitted with all their new chemicals, the data are used principally to classify and label the chemicals according to a set scheme. This is in contrast to the US practice where hazard information is evaluated and integrated with potential exposure to ascertain risk. In addition, under the EC scheme additional testing on the new chemical must be provided as production grows (known as the "step system"). In the US, on the other hand, if controls or testing requirements are not implemented before manufacture commences, the new chemical authorities under TSCA no longer apply. Thus any controls or testing must be done under TSCA's existing chemical provisions which carry a much heavier burden for the government. Thus the emphasis on end-points tends to differ under the two schemes, with more weight given to acute effects (i.e. lethal dose, eye and skin irritation and sensitisation) in the EC scheme and more attention paid to long-term or sub-chronic effects in the US, with relatively little emphasis given to acute effects. Nonetheless, because the US does not routinely predict acute effects for new chemicals (end-points which are well represented in the MPD), but focuses its efforts on predicting long-term effects (many of which are not covered by the MPD), the study was somewhat limited in its ability to compare health hazard predictions with MPD results. These points will be discussed in more detail below.

For the analysis of the comparison between predicted effects and test data, each end-point was compared and analysed separately. An overall analysis was also done which attempted to compare the US and EC "bottom line" health assessments for each chemical regardless of effect.

For acute effects the US predictions corresponded to the EC results between 78-88% of the time. Eye irritation had the lowest correspondence between predicted and measured value and dermal irritation had the highest. Nonetheless, irritation and sensitisation are not judged to be particularly amenable to SAR analysis except for general classes; furthermore the tests for these effects are, in general, inexpensive. It seems reasonable that if understanding of these effects is an important consideration under a given scheme, then the submission of data is preferable to prediction. For acute toxicity, the predictive approach worked reasonably well and is judged to be acceptable for screening purposes (i.e., qualitative assessment).

Overall, for mutagenicity the US predictions corresponded to the EC results 94% of the time. Out of 144 data sets available for mutagenicity, 21 initially were in disagreement between the US prediction and the EC results. Further analysis of the 21 revealed that three of the disagreements were due to the use of inappropriate analogues by the US, two were due to lack of positive analogue data and weak or marginal positive responses reported in the EC data, and four were due to the absence of analogue mutagenicity data upon which to base SAR decisions. The remaining 12 may be MPD "false negatives" caused by testing in assay systems known to be insensitive to specific classes of chemicals. These 12 were called positive by the US due to analogue data reporting positive results in assay systems known to be sensitive to chemicals in the specific classes. Six chemicals with positive results were predicted "low" because of the lack of data on analogues and an absence of structural features suggestive of mutagenic activity. These false negatives, while small in number, were of concern and suggest that testing for this end-point should be considered in cases for which data on analogues are unavailable and exposures are projected to be at moderate or higher levels.

For long term and sub-chronic effects, the US routinely predicts systemic toxicity as well as developmental and reproductive toxicity, neurotoxicity, and oncogenicity. The EC "base set" data includes only a 28-day repeat-dose study which does not address the latter concerns. In order to analyse the results of the study, systemic toxicity was assessed and then the concerns that fall outside of the 28-day study were folded into the analysis to achieve an overall analysis of the US predictions.

Systemic toxicity, exclusive of developmental and reproductive toxicity, neurotoxicity, and oncogenicity, was analysed by comparing the US predictions (concern levels)[3] for systemic toxicity only with the MPD data; both were also scored according to severity of effect which was predicted/observed. The results of this analysis showed that for 57% of the 138[4] chemicals assessed the scores were identical and for 43% the scores disagreed. Further analysis revealed that the US tends to under-predict systemic toxicity (effects and/or severity) as observed in the MPD's 28-day study (which, in itself, is judged to provide a reasonable approximation of sub-chronic toxicity for most chemicals). For 27% of the chemicals, the US predicted a "low" concern whereas the MPD 28-day study supported a "low-moderate" or greater concern level. For 3% of the cases, the US predicted some concern (i.e., low-moderate or greater) while the MPD results supported a higher level of concern. For 14% of the cases, results of MPD testing supported a lower level of concern than was predicted by the US; in 11% of the cases the MPD supported a "low" concern whereas the US predicted low-moderate or greater concern. Note, however, that while the comparison study suggests a clear tendency to underestimate rather than overestimate the potential for systemic toxicity, the magnitude of the difference between the US and EC calls was relatively small. For example, in 23 of the 41 cases for which the US under-predicted the concern level, the MPD supported a "low-moderate" concern whereas the SAR-based call was for "low" concern while in 3 additional cases where the US predicted "low-moderate" or greater concern, the MPD supported a one-step increase in the concern level (e.g., "low-moderate" concern to "moderate" concern). This, nonetheless, is interpreted as indicating that the US needs to exercise caution in interpreting systemic toxicity predictions and should consider requiring a repeat dose test in cases where the projected exposures are at moderate or higher levels.

When concerns not addressed by the MPD (i.e., developmental and reproductive toxicity, neurotoxicity, and oncogenicity) were folded into the analysis, the US level of concern scores were identical to the MPD scores 78% of the time. The chemicals for which non-MPD health concerns were identified by the US were analysed to determined the nature and frequency of their occurrence. Of the 143 chemicals, 66 had concerns identified by the US that suggested one or more health effects beyond the scope of the MPD. The breakdown by predicted effect revealed that 32% of the chemicals had developmental toxicity concerns, 23% had oncogenicity concerns, 15% had neurotoxicity concerns, and 9% had reproductive toxicity concerns.

The large number of chemicals that were predicted to have effects not addressed by the MPD raises the issue of possible improvements to the MPD. Although it may not be feasible to address oncogenicity directly, the developmental, reproductive and neurotoxicity concerns could conceivably be screened by use of a modified testing scheme. Thus, in designing a "base set" of testing, it may be appropriate, given the relative frequency with which these potential effects were identified in this study, to include testing to screen for these effects.

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[3]The concern levels employed by the US in assessing new chemicals (and used in this study) are as follows: low, low-moderate, moderate, moderate-high, and high.

[4]Five of the chemicals were not tested in a 28-day study due to physical/chemical properties (e.g., pyrophoric) that rendered them unsuitable for testing.

When overall level of concern scores for health effects are considered, (i.e., a bottom-line assessment considering all effect areas), the trend towards under-prediction rather than over-prediction (which was observed in the analysis of systemic toxicity outcomes) is still apparent. If the overall level of concern scores are analysed similarly to the systemic toxicity scores, 11% of the chemicals were identified by the US as being of low concern whereas the MPD supported a low-moderate or greater concern based on the MPD data, while an additional 8% were identified as being of low-moderate or greater concern by the US while the MPD supported a higher level of concern. In contrast, for only 4% of the cases did the MPD support an overall lower level of concern than had been projected by EPA. However, the scores for overall level of concern for health effects indicate a higher concordance between the US and EC than scores that were seen in the systemic effects analysis, which is due in part to the inclusion of concerns expressed for other MPD end-points (e.g., mutagenicity) as well as effect end-points outside the scope of the MPD "base set".

5.1.2.4. Ecotoxicity

When the EPA predicted fish and daphnid acute toxicity levels of concern were compared to the levels of concern assigned to the MPD measured acute values, the agreement (± 1 order of magnitude) for fish acute toxicity was 82% (107 chemicals) and for daphnid acute toxicity 71% agreed (90 chemicals). The number of chemicals in the EC data sets having fish and daphnid toxicity differed from each other with 139 chemicals tested for fish toxicity and 137 chemicals tested for daphnid toxicity. For fish toxicity the US tended to over-predict toxicity rather than under-predict (11% versus 7%); for 7% of the chemicals the US predicted a "moderate" level of concern[5] whereas the MPD data set supported a "low" concern, for 4% of the chemicals the US predicted a "high" concern and the MPD data set supported a "low" concern, and for 5% of the chemicals the US predicted a "high" level of concern and the MPD data set supported a "moderate" level of concern. Under-prediction resulted in 6% of the chemicals having their fish toxicity scores raised from a "low" concern to a "moderate" concern and 1% going from a "moderate" concern to a "high" concern.

In contrast, for daphnid toxicity over- and under-prediction of toxicity values occurred at about the same rate (16% versus 13%). The greatest percentage of chemicals (15%) where the US prediction was not supported by MPD data occurred with chemicals the US considered as "low" concern, while the MPD data supported a "moderate" concern level. In only 3% of the cases were the daphnid concern scores raised from a "low" concern to a "high" concern.

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[5]For aquatic toxicity the concern levels are expressed as "high," "moderate," and "low" according to the following criteria:

- Acute toxicity values < 1mg/l and/or chronic toxicity values < 0.1mg/l receive a high concern.
- Acute toxicity values from 1 to 100mg/l and/or chronic toxicity values from 0.1 to 1mg/l receive a moderate concern.
- Acute toxicity values > 100mg/l, chronic toxicity values > 1mg/l, and cases where the solubility is severely limited and no effects are anticipated at saturation receive a low concern.

Potential reasons for the under- and over-prediction in both species were investigated and appeared to be largely the same. These reasons include: reported LC50 above water solubility, use of nominal concentrations for chemicals having significant volatility from water, water solubility enhancement with a solvent, impurities, and apparent poor solution preparation. When the EC chemicals having questionable data were removed from the data set, the agreement between the US predicted values and the EC measured values is 87% for fish acute toxicity and 79% for daphnid acute toxicity.

One advantage of the US SAR methods over the MPD data set is that the US SAR analysis evaluates all of the potential effects and concerns of a chemical, e.g., acute and chronic toxicity to fish, aquatic invertebrates, and green algae, including benthic organisms, aquatic insect, and submerged aquatic vegetation. In addition, potential effects to terrestrial organisms, e.g., birds, earthworms, insects, vascular plants, and soil microbes, are evaluated. The MPD for environmental effects is restricted at present to fish and daphnid acute toxicity tests.If the overall EPA level of concern is compared with the level of concern for acute fish toxicity as measured by the MPD data set, there is concordance in 54% of the chemicals. Further analysis of these data reveals that in 28% of the non-concordant cases, the driving concern was for algal toxicity and in 8% of the cases, chronic effects were the major concern; these effects are not included in the MPD data set. Comparing the overall EPA level of concern with the level of concern supported by the MPD data for each chemical, the trend towards over-prediction of toxicity becomes clear (42% or 59 chemicals). However, recall that if only fish toxicity levels of concern are compared, the over-prediction falls to 16%.

If the overall EPA level of concern is compared with the level of concern for acute daphnid toxicity 24-hr EC50 values as measured by the MPD data set, there is concordance in 54% of the chemicals. Further analysis of these data reveals that in 14% of the non-concordant cases, the driving concern was for algal toxicity, in 6% of the cases chronic effects were the major concern and in 9% of the cases the predicted value was for a 48-hr EC50 instead of the MPD 24-hr EC50. Again as with the fish values, if the overall EPA level of concern for daphnid toxicity is compared with the level of concern supported by the MPD data, the trend towards over-prediction of toxicity is again apparent (37%, 51 chemicals). As with the fish acute values, if only the daphnid toxicity levels of concern are compared, the over-prediction falls to 23%.

These analyses demonstrate that in a significant number of cases the driving concern for the US was an effect outside of the MPD data set; this suggest that the MPD data set may be improved by expanding the end-points included in the MPD. The addition of the algal toxicity test would allow the MPD data set to identify chemicals which show their greatest effects toward algae and plants, while the addition of the daphnid reproductive toxicity test would give the MPD a greater chance of identifying chemicals causing chronic toxicity.

5.1.2.5. Other considerations

Several additional factors, specifically chemical purity, classes of chemicals included in the MPD set, and the summary nature of the MPD data, may have added uncertainty to the study that was not possible to quantify.

Unlike the US which requires pre-manufacture notification, the EC requires pre-marketing notification. For US pre-manufacture notification, the notified chemical is most often submitted as a "pure" compound (i.e., 95% or greater purity), while for EC pre-marketing notification, the notice pertains to the substance "as marketed," which is often a formulated product (i.e. a mixture containing other chemicals or solvents). This distinction has important implications for the predictability of physical/chemical properties, biodegradation, and potential hazard concerns. In the US, the new chemical and any impurities reported by the submitter and/or identified as being likely contaminants by the EPA are considered when assessments are performed. In the EC, the submitter is required to

provide purity information for the product as marketed and any test data pertain to this product. Although in only one case did this distinction result in a large disparity in predicted systemic toxicity versus experimentally determined systemic toxicity, more subtle disparities may not be easily discerned. Clearly, in the physical/chemical properties exercise, this difference in chemical substances played a not insignificant role in differing results between predicted values and experimental values. The study, however, suggests that the US should consider requiring purity tests for PMN chemicals which are subjected to EPA-required testing. The purity analysis should be conducted on the new chemical as produced via commercial production processes (i.e., characterize the commercial chemical not a research and development (R&D) sample which may differ significantly from the commercial substance).

Although the EC chemicals provided a wide range of chemical classes, the number of chemicals in each class and the classes themselves were not wholly representative of the numbers and classes that are typically reviewed by the US. For example, the EC does not routinely review polymer chemicals, so few polymers were included in the study. On the other hand, the EC scheme includes pesticide active ingredients and pharmaceuticals. In the US new chemicals scheme, such chemicals are reported under TSCA only if they have TSCA uses (e.g., industrial or consumer uses). Thus, pesticides and pharmaceuticals occurred with greater frequency in the MPD set of chemicals than would be expected in a typical equivalent set of US new chemicals. Thus, the experience and expertise of the US new chemical assessors was not a "perfect fit" for some of the EC chemicals and the skewed frequency of the classes of chemicals may have affected the US performance in this study.

Lastly, the data from the EC were available to the US only in summary form. The original data were reviewed and a summary was prepared by the Competent Authority in the EC country of origin. These summaries varied widely in the level of detail, so the US assessors were limited in their ability to interpret results independently. While most likely not a limiting factor in the interpretation of overall (qualitative) levels of concern, it may have been a factor in the quantitative determination of the level of toxicity.

5.1.3. Summary

Looking at the overall results of the MPD/SAR study, it is interesting to note that overall the physical/chemical properties appear to be the most difficult to predict accurately, but are among the most inexpensive to measure. On the other hand, predicting of health hazards appears reasonably good, although there is an issue as discussed above, with the prediction of systemic toxicity. Targeted testing may offer a cost effective alternative to use of a standard test battery. US ecotoxicity predictions appear to be reasonably accurate in assessing acute toxicity for fish and daphnia.

The MPD/SAR study provided a unique opportunity to gain insight into the strengths and weaknesses of the SAR approach used by the US versus the MPD approach of the EC in assessing the potential fate and effects of new chemicals. Analysis of the results of this study have shown that while the SAR approach has largely been successful in identifying chemicals of concern, the process could be improved by selectively incorporating specific testing schemes into the process. Results from such schemes would serve two purposes: to gain insight into chemical toxicities and to improve our predictive capabilities. Improving predictive capabilities would result in better hazard assessment for new chemicals by providing a richer data base upon which to base predictions as to their fate and effects. These enhanced capabilities would also serve to avoid questionable testing requirements and thus spare manufacturers the cost of such testing while not compromising worker, consumer or environmental safety. Such a focussed effort would provide valuable data while not presenting large overall cost implications.

5.2. Conclusions: EC perspective

5.2.1. Introduction

This study has provided many useful insights into the strengths and weaknesses of the notification scheme for new chemicals established under Directive 67/548/EEC as amended. The results will be taken into account in the preparation of any future modification to the MPD or "base set" used for the notification or chemicals marketed in quantities in excess of 1 tonne per annum. In addition to the direct benefits which will result from the project, the study also allowed the Commission and the national authorities in the Member States to obtain a better understanding of the PMN system as applied in the United States under TSCA. While the benefits which accrue from such improvements in mutual understanding are less tangible and difficult to quantify, they are nonetheless real and will certainly facilitate the development of a more global approach to chemicals control in-line with the objectives set out in Chapter 19 of Agenda 21 of UNCED.

5.2.2. Synopsis

5.2.2.1. Physico-chemical end-points

Of the three end-points which were adequately explored, the SAR methods performed best in relation to log P_{ow}. However, even for this end-point, the predictive methods could not be used with confidence for all chemical groups. Given the relatively low cost of carrying out these tests, the results of this project do not constitute a persuasive argument for introducing SAR into the "base set" as an alternative to testing.

5.2.2.2. Biodegradation

The SAR methods performed extremely well in relation to this end-point, and at the next revision of the "base set", consideration should be given to allowing, under defined conditions, the estimation of biodegradation using SAR.

5.2.2.3. Health effects

The SAR methods are not sufficiently developed in relation to the estimation of eye/skin irritation or sensitisation. As knowledge about these end-points is an essential part of the EC notification scheme, testing for these parameters will continue. SAR techniques were, in contrast, relatively successful in providing qualitative assessments of acute lethal toxicity, and the opportunity for building SAR into a future battery of approaches - including SAR, in vitro tests and non LD50 animal tests - should be explored.

While the SAR methods displayed a tendency to underestimate sub-chronic 28-day, repeated dose toxicity, in most cases this involved an underestimate of the severity of the effects rather than true, "false negatives". At the present time, it is unlikely that the testing requirements for sub-chronic/repeated dose toxicity in the "base set" will be modified. However, it is clear that the SAR techniques provide an excellent additional tool for informing decisions about further testing either immediately post "base set" or at level 1/level 2, as foreseen in the Directive.

With regard to mutagenicity, the results of this project would suggest that SAR could, in a future revision of the "base set", usefully be incorporated into a battery of approaches for evaluating the mutagenic potential of a new chemical. In particular, the issue of the apparent 'false negatives' given by the current "base set" testing package needs to be addressed.

The proportion of substances in the test sample which were predicted as being of concern in relation to end-points not covered by the 6th Amendment "base set", e.g. reproductive toxicity, developmental toxicity, carcinogenicity and neurotoxicity is a considerable source of disquiet. The 7th Amendment to the Directive does foresee the introduction into the "base set" of a screening test for reproductive toxicity. In the light of this project, consideration should also be given to addressing the other "missing" end-points.

5.2.2.4. Ecotoxicity

The SAR methods performed extremely well in predicting acute toxicity to fish and daphnia. They also provided estimates of toxic effects e.g. algal toxicity, not addressed in the "base set" of the 6th Amendment. As part of any future revision, the conditions under which SAR predictions of acute toxicity to aquatic organisms could be integrated into the "base set", should be explored.

5.2.3. Overview

As indicated in the preceeding section, this project has identified a number of possibilities for making greater use of SAR as part of the "base set" testing package applied to new chemicals marketed in the European Community. These possibilities will be explored in the preparation of any future revision to the legislation. However, in contemplating any such revision, there are a number of factors which should also be taken into account.

1) The EC system is operated in a decentralized manner across 12 different national authorities: this figure will shortly be increased to 16 when the EFTA countries join the scheme in the context of the Enlarged European Economic Area. This means that any approach to notification has to be transparent and objective. Thus, while some SAR methods may be used successfully by a group of highly skilled experts working together over many years in one Agency, such an approach could not work in the decentralized system applied in the EC. This means that opportunities for the (consistent) systematic introduction of SAR into the EC scheme could only be considered where the predictive models could be applied objectively by all agencies working within the decentralised system.

2) The EC Directive puts great importance on the classification of a chemical. The emphasis given to classification is frequently misunderstood because the term classification is almost invariably linked with the term labelling, thereby giving the impression that labelling is the only purpose for which substances are classified : this impression is entirely false.

   Classification means the allocation of a substance to one of a number of danger categories on the basis of its intrinsic properties. The decision to allocate substances to a particular category is based on a series of agreed and published criteria. Classification is therefore synonymous with the term hazard/risk identification. Within the EC, classification is consequently the foundation for hazard assessment and the recently agreed Commission Directive laying down the general principles for the risk assessment of new chemicals, recognises classification as providing the starting point for hazard/risk assessment. Secondly, classification may also be the basis for risk reduction: substances classified as carcinogens under the EC scheme are for

example subject to severe restriction in the work place under separate EC legislation. Finally, classification is also the basis for the system of hazard communication by means of standardized labels which has been developed in the EC.

Given the critical importance of classification for the entire EC policy on chemicals, it is essential that the current approach to classification on the basis of objective, transparent criteria is not put into question by allowing the possibility of using SARs instead of test data. Essentially this would mean that SARs could be only admitted :

- if they were objective and reliable and
- if they were able to generate precise quantitative estimations/predictions of test results which could be incorporated into classification schemes or
- if notifiers accepted the principle that classification on the basis of SARs would be admitted but escape from classification i.e. non-allocation to a danger category would not be allowed.

3) The EC notification scheme is directed towards the substance as marketed, including impurities but excluding separable solvents and any non essential stabilizers. The notification scheme is not concerned with purified substances nor is it concerned with formulated products (preparations). While it is clear that the SARs used in this study have in many cases performed very well, such predictive models are in the most part, based upon pure substances. For SARs to be used in a systematic way in the context of the EC notification scheme would require this important issue of impurities to be addressed.

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COMPANIES, WHICH GAVE PERMISSION TO USE THEIR SUBSTANCE'S DATA WITHIN THE US EPA/EC PROJECT ON SAR

3M
AGFA GEVAERT
AGFA GEVAERT AG
AH MARKS & Co Ltd
AKZO CHEMIE
AKZO CHIMICA SPA
AVONDALE CHEMICAL COMPANY
BASF
BENTONE-CHEMIE GmbH
BOEHRINGER INGELHEIM KG
BOEHRINGER MANNHEIM GmbH
BUSH BOAKE ALLEN Ltd
CECA
CHEMISCHE FABRIK STOCKHAUSEN GmbH
CHIMEX
CIBA GEIGY
CIBA GEIGY A/S
CIBA GEIGY DANMARK
CIBA GEIGY D&C
CIBA GEIGY GmbH
CIBA GEIGY INDUSTRIAL CHEMICALS
CIBA GEIGY MARIENBERG GmbH
CIBA-GEIGY PLASTICS
CONTINENTAL PHARMA
CYANAMID BV
DEUTSCHE EXXON CHEMICAL GmbH
DEVELOP DR. EISBEIN GmbH&Co
DOMUS IND. CHIM.
DOW CORNING Ltd
DSM CHEMICALS
DSM RESINS B.V.
DU PONT DE NEMOURS
DU PONT DE NEMOURS (DEUTSCHLAND) GmbH
E. MERCK
ENICHEM SYNTHESIS
EPSON DEUTSCHLAND GmbH
EPSON FRANCE
ERGAM RONEO
FARCHEMIA SRL
FORMICA
FRAT. LAMBERTI
FUJI HUNT
FUJI PHOTO FILM BV
GALVANOCOR (GB) Ltd
GOODYEAR CHEMICALS
GRACE SERVICE CHEMICALS GmbH
GREAT LAKE CHEMICALS (EUROPE)

HAAG TECHNO BV
HERCULES
HIMONT ITALIA SPA
HOECHST AG
INTERNATIONAL PAINT p.i.c.
ISF
ISF SPA
JANSSEN PHARMACEUTICA
KODAK PATHE
KRONOS SA/NV
LAGOR SPA PROD. CH.
LONZA FRANCE
LONZA ITALIA SPA
LONZA-WERKE GmbH WALDSHUT
LUBRIZOL FRANCE
LUBRIZOL Ltd
LUPEROX GmbH/MAP
MERCK, SHARP & DOHME
MINOLTA CAMERA HANDELSGES. mbH
MOBIL OIL Co Ltd
MONSANTO
MONTEDISON SPA
N L ABBEY CHEMICALS Ltd
OLIN HUNT
PALMAROLE
PANASONIC
PANASONIC DANMARK A/S
PANASONIC DEUTSCHLAND GmbH
PANASONIC ITALIA
POLAROID (EUROPA)
PROCTER AND GAMBLE LIMITED
Q.O CHEMICALS INC
RHONE POULENC
RICOH EUROPE
RICOH FRANCE
RICOH NEDERLAND
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GENERIC CHEMICAL DESCRIPTIONS OF THE CHEMICALS IN THIS PROJECT

Chemical	Description
4	alkyl aluminium, halogenated complex
6	aryl dialkyl ammonium clay complex
16	mixture of bis-(hydroxyalkylammonium) salts of fatty acids
17	reaction mixture of unsaturated fatty acids, imino-dialcohol and inorganic acid
21	complex haloaryl alkylamide
23	substituted alkali pyrazoline arylsulfonate
24	phenolic benzopyran derivative
26	substituted spiro bis-indane
37	aryl substituted alkyl dione
44	perhalo polycyclic hydrocarbon
47	alkyl hydroquinone
49	phosphorodithionic aliphatic amine
50	halogenated polymer of polyalkylmethacrylate
53	complex alkyl ester of a diaza-spiro carboxylic acid
54	thioaryl morpholine ketone
61	haloaryl acetanilide
68	halotriazine dye
69	halotriazine azo dye
70	haloaryl anilide
76	mixture of aryl (substituted benzotriazole) esters of polyethylene glycol
78	azo dye
79	aryl organo-nickel complex

Chemical	Description
87	substituted phenol
96	azo dye
99	trialkoxy vinyl silane
101	halotriazine dye
102	bis-(dialkyl)aryl-substituted peralkyl phenol
106	bis-(bicycloalkyl) alkane
107	alkyl substituted siloxy aluminium
108	halogenated alkylaryl silane
107	dialkyl carbonate
113	alkyl alkoxybenzene di-alkyl valerate
118	alkyl amino triazole
124	haloaryl silane substituted triazole
128	haloaryl substituted pyrazole
133	pyrazole substituted with various aryls
144	alkoxy aryl quinoline
148	substituted polyaromatic hydrocarbon
151	bisphenol A derivative
155	mixture of various substituted benzotriazoles
156	alkyl substituted aryl thiocarbamate
164	phosphothioalkylamide mixture
170	N-arylalkylamino acetophenone hydrochloride
173	mixture of aryl tertiary amines
176	alkylamino chain substituted with piperidine and triazine
182	calcium alkyl aryl sulfonate
186	haloaryl substituted triazole

Chemical	Description
192	mixture of esters of alkane phosphinic acid
194	pyrazole substituted with various aryls
196	halotriazine dye
197	haloalkylphenoxy aminoaryl aniline hydrochloride
200	halo substituted diaryl alkane
204	variously substituted haloacetanilide
214	partially quaternised arene,tallow carbamate
216	substituted bis-(cycloalkene) iron
217	aryl pyrrolopyrroledione
218	cycloalkyl alkyl substituted xylene
219	haloalkoxy arene
222	aryl substituted alkylisocyanate
224	phenoxodiazine dye
235	alkyl aminoalkyl substituted benzothiazolethione
237	alkoxy alkyl silane
239	alkylamino arene substituted halophthalide
240	halotriazine dye
241	alkyl pyridinium halide
242	alkyl pyridinium halide
253	thioalkyl cresol
256	amino acid amide
263	chromium azo dye
265	haloacetyl amino acid derivative
267	haloaryl-ketone polymer
268	alkylamino carboxylic acid, Cn(medium chain)halo-alkyl ester

Chemical	Description
269	substituted alkyl styrene polymer
270	alkyl piperidine succinate
271	mixed sodium salts of aminocarboxylic acid
275	nitroaryl azo dye
278	mixed isomers of a terpene carboxylate
281	diaryl ketone
283/429	mixture of perhaloalkyltetraoxodecanates
286	halo alkyl alkoxy aryl sulfonamido substituted pyrazolo-triazol
287	alkyl aryl sulfonamide substituted indole
289	azo nitrobenzoate dye
291	azo dye
292	haloaryl alkyl silyl triazole
300	arylpropionate alkyl ester
307	haloalkoxy nitroaryl
309	diaryl substituted aryl diamine
312	alkyl diol substituted arylamine
318	azo dye, calcium salt
320	nickel complex of oxyiminopolyaryl
321	substituted triazine trione
330	carboxyalkyl amino acid
335	chromium azo dye, alkyl ammonium salt
336	aluminium tris alkylphosphonate
337	haloalkyl phosphate tri-ester
340	cyano-alkyl thiazole
341	thia lactam derivative

Chemical	Description
342	alkylene carbonate
344	arylacetoacetate alkanolamine salt
348	aryl substituted urea
349	aryl substituted anthracenedione
354	alkyl alkoxyaryl carbamate
355	methacrylic acid, aryl ester
360	aryl alkyl carboxylate
361	alkyl imidazolidine substituted halobenzoate
362	aryloxyalkyl tosylate
364	halotriazine azo dye
366	alkenyl substituted polysiloxane
368	alkylalkoxy silane
369	ferric ammonium salt of carboxyalkyl amino acid derivative
370	haloalkene carbonate
373	C10-terpene
376	condensation mixture of alkylphenol, formaldehyde and alkane thiol (alkylthioalkylaryl substituted methylene bis-(alkylaryl))
379	branched alkene
381	substituted phenoxazine pigment
383	aryl triazine trione
386	aryl alkenyl morpholine
393	alkyl amino acridindione
394	potassium salt of substituted amino acid
396	substituted imidazole
398	cycloalkyl alkoxy silane
401	chiral aryl arylamide dibenzoyl tartrate

Chemical	Description
406	aryl glycidyl ether
411	haloaryl azo dye, calcium salt
413	dialkyl ester of alkyl disulfide
414	hexahydro aromatic carboxylate, ammonium salt
415	pyrazole substituted arylsulfonamide
416	aryl substituted naphthyl ketone
417	spiro naphthoxazine
420	halo alkoxy benzophenone
421	aryl aminoalkenyl ester sulfone
425	alkylamino alkanol
431	haloaryl alkyl carbonate
436	alkylammonium alkylphosphonate
437	mixture of substituted thiadiazoles
439	sulfonated styryl biphenyl
441	alkyl substituted heterocyclic amine hydrochloride
442	sulfonated vinylic acetamide
443	aza bicyclo alkane
444	heterocyclic ester of methacrylic acid
445	copolymer of methacrylic acid and heterocyclic ester of methacrylic acid
446	aryl substituted thiazole
451	alkoxy alkyl ester of unsaturated carboxylic acid
472	alkoxyalkyl tetradecanoate

BOILING POINT: COMPARISON OF TEST RESULTS AND PREDICTIONS

Chem. No.	MPD Boiling point [°C]	SAR Boiling point [°C]	Result
4	(decomposes)	nd	-
6	nd	>500	-
16	>225 (decomposes)	>500	disagree
17	5 (decomposes)	nd	-
21	175 (decomposes)	>500	disagree
23	nd	>500	-
24	nd	~400	-
26	nd	500	-
37	295 (100 kPa)	nd	-
44	213 - 217	nd	-
47	>210 (250Pa)	nd	-
49	145 (decomposes)	nd	-
50	300 (decomposes)	(decomposes)	-

Chem. No.	MPD Boiling point [°C]	SAR Boiling point [°C]	Result
53	>260	nd	-
54	349	210 (Beilstein)	-
61	nd	nd	-
68	nd	nd	-
69	nd	nd	-
70	>220 (2Pa)	nd	-
76	>400	nd	-
78	nd	nd	-
79	nd	nd	-
87	nd	350	-
96	nd	nd	-
99	258.5	285	agree
101	nd	nd	-

Chem. No.	MPD Boiling point [°C]	SAR Boiling point [°C]	Result
102	217 (11Pa)	nd	-
106	>250	345	disagree
107	122 (0.07kPa)	nd	-
108	>300	200 - 300	agree
110	215	378	disagree
113	238	570	disagree
118	109 (11Pa) (>275)	>300	agree
124	214 (decomposes)	nd	-
128	nd	>350	-
133	nd	nd	-
144	322 (decomposes)	nd	-
148	nd	nd	-
151	255 (decomposes)	420	disagree

Chem. No.	MPD Boiling point [°C]	SAR Boiling point [°C]	Result
155	174 (11Pa)	-	-
156	129 (33.3Pa)	-	-
164	210 - 230 (decomposes)	nd	-
170	>198 (decomposes)	nd	-
173	nd	nd	-
176	nd	nd	-
182	>360 (decomposes)	nd	-
186	nd	nd	-
192	216	190	agree
194	nd	nd	-
196	nd	nd	-
197	nd	nd	-
200	190 (93Pa)	374 (Beilstein)	-

Chem. No.	MPD Boiling point [°C]	SAR Boiling point [°C]	Result
204	230 (40Pa) (decomposes)	>400	agree
214	160 - 170 (decomposes)	nd	-
216	nd	nd	-
217	nd	nd	-
218	105 - 245	175 (10 torr) (>350)	disagree
219	250	276 (Beilstein)	-
222	268	263	agree
224	nd	nd	-
235	335	nd	-
237	177	180	agree
239	nd	nd	-
240	nd	nd	-
241	>204 (decomposes)	nd	-

Chem. No.	MPD Boiling point [°C]	SAR Boiling point [°C]	Result
242	212-214	nd	-
253	> 178 (11Pa)	≥416 (178, 0.083 torr)	agree
256	nd	nd	-
263	nd	nd	-
265	nd	nd	-
267	nd	nd	-
268	197	> 400	disagree
269	> 300	nd	-
270	> 400	> 400 (Beilstein)	-
271	160 (decomposes)	≥500	disagree
275	nd	nd	-
278	> 300	351 (153-154, 0.1 torr) (Lit. value)	-
281	> 300	318 - 320 (Beilstein)	-

Chem. No.	MPD Boiling point [°C]	SAR Boiling point [°C]	Result
283/ 429	213	210 - 215 (Beilstein)	-
286	150 (decomposes)	nd	-
287	210 (decomposes)	nd	-
289	nd	nd	-
291	nd	nd	-
292	>248 (decomposes)	nd	-
300	300	336	agree
307	266	nd	-
309	>170 (decomposes)	nd	-
312	>171 (decomposes)	nd	-
318	nd	nd	-
320	nd	(decomposes)	-
321	325	nd	-

Chem. No.	MPD Boiling point [°C]	SAR Boiling point [°C]	Result
330	>150	nd	-
335	nd	nd	-
336	nd	nd	-
337	203	≥330	disagree
340	nd	(decomposes)	-
341	nd	>463	-
342	241	247	agree
344	nd	nd	-
348	nd	nd	-
349	nd	nd	-
354	nd	nd	-
355	nd	nd	-
360	360 (extrapol.)	>400	agree

Chem. No.	MPD Boiling point [°C]	SAR Boiling point [°C]	Result
361	175 - 179 (13.3 Pa)	nd	-
362	254 (decomposes)	>250 (1 torr)	agree
364	nd	nd	-
366	>400	nd	-
368	188	190	agree
369	nd	nd	-
370	165	155 (Beilstein)	-
373	193 - 204	188 (Beilstein)	-
376	215 - 220 (start to decompose at 191)	>500	disagree
379	142 - 143	143.5 - 144 (Beilstein)	-
381	nd	nd	-
383	nd	nd	-
386	nd	(decomposes)	-

Chem. No.	MPD Boiling point [°C]	SAR Boiling point [°C]	Result
393	nd	(decomposes)	-
394	nd	(decomposes)	-
396	nd	nd	-
398	246	nd	-
401	nd	nd	-
406	> 300	nd	-
411	nd	nd	-
413	375	400	agree
414	(decomposes)	nd	-
415	> 224 (decomposes)	> 300	disagree
416	> 187 (decomposes)	(decomposes)	-
417	nd	nd	-
420	nd	300 - 370	-

Chem. No.	MPD Boiling point [°C]	SAR Boiling point [°C]	Result
421	247 (decomposes)	nd	-
425	222 - 226	216	agree
431	188 - 190 (133 Pa)	(decomposes)	-
436	268	(decomposes)	-
437	182	>300	disagree
439	nd	nd	-
441	nd	nd	-
442	205 (decomposes)	nd	-
443	134	82.5 - 83 (Beilstein)	-
444	335	245	disagree
445	nd	nd	-
446	nd	nd	-
451	93 - 193 (decomposes)	274	disagree
472	>300 (decomposes)	nd	-

VAPOUR PRESSURE: COMPARISON OF TEST RESULTS AND PREDICTIONS

Chem. No.	MPD vapour pressure	SAR vapour pressure [torr]	Difference (pred./meas.) [+ log units]	Result
4	5,200 Pa 39 torr	$<10^{-3}$	-4.6	disagree
6	nd	$<10^{-6}$ [10^{-6}]	-	-
16	<7Pa (25°C, 65°C) 5.25 x 10^{-2} torr	$<10^{-5}$	-3.7	disagree
17	7Pa (24°C, 65.5°C) 5.25.10^{-2} torr	$<10^{-4}$	-2.7	disagree
21	<0.1 Pa (<170°C) [10^{-6} torr at rt]	$<10^{-6}$ [10^{-6}]	0	agree
23	<0.01 Pa 7.5 x 10^{-5} torr	$<10^{-5}$	-0.8	agree
24	10^{-4} Pa [10^{-6} torr]	$<10^{-6}$ [10^{-6}]	0	agree
26	10^{-4} Pa [10^{-6} torr]	$<10^{-6}$ [10^{-6}]	0	agree
37	3.27 Pa 0.0245 torr	0.0245	0	agree
44	133.2 Pa at 70°C 10^{-1} torr at rt	0.11	0.04	agree
47	$<10^{-3}$ Pa 7.5 x 10^{-6} torr	$<10^{-8}$ [10^{-6}]	-0.8	agree
49	68 Pa 0.51 torr	$<1.4 \times 10^{-4}$	-3.5	disagree
50	nd	$<10^{-8}$ [10^{-6}]	-	-

Chem. No.	MPD vapour pressure	SAR vapour pressure [torr]	Difference [± log units]	Result
53	6.7×10^{-5} Pa [10^{-6} torr]	$\leq 10^{-6}$ [10^{-6}]	0	agree
54	2×10^{-7} Pa [10^{-6} torr]	3.3×10^{-3}	+3.5	disagree
61	< 10 Pa 7.5×10^{-2} torr	$< 10^{-7}$ [10^{-6}]	-4.8	disagree
68	nd	$< 10^{-8}$ [10^{-6}]	-	-
69	nd	10^{-7} [10^{-6}]	-	-
70	-	$< 10^{-6}$ [10^{-6}]	-	-
76	4.8×10^{-5} Pa [10^{-6} torr]	10^{-6} [10^{-6}]	0	agree
78	nd	$< 10^{-8}$ [10^{-6}]	-	-
79	nd	$< 10^{-7}$ [10^{-6}]	-	-
87	6.04×10^{-4} kPa 4.53×10^{-3} torr	2.34×10^{-3}	-0.3	agree
96	nd	$< 10^{-6}$ [10^{-6}]	-	-
99	0.026 kPa 0.195 torr	0.0054	-1.5	disagree
101	nd	$< 10^{-8}$ [10^{-6}]	-	-

Chem. No.	MPD vapour pressure	SAR vapour pressure [torr]	Difference [± log units]	Result
102	2.10^{-13} kPa [10^{-6} torr]	10^{-5}	+1.0	agree
106	0.024 Pa 1.8×10^{-4} torr	2.5×10^{-4} torr	+0.1	agree
107	1.49×10^{-4} kPa 1.12×10^{-3} torr	<0.01	+0.9	agree
108	18×10^{-2} Pa 1.35×10^{-2} torr	≤0.023	+0.2	agree
110	1.03×10^{-5} Pa [10^{-6} torr]	10^{-5}	+1.0	agree
113	2.6×10^{-5} Pa [10^{-6} torr]	$<10^{-6}$ [10^{-6}]	0	agree
118	7.1×10^{-6} kPa 5.34×10^{-5} torr	10^{-5}	-0.7	agree
124	3.3×10^{-4} Pa 2.47×10^{-6} torr	10^{-8} [10^{-6}]	-0.4	agree
128	nd	$<10^{-6}$ [10^{-6}]	-	-
133	9.6×10^{-7} kPa [10^{-6} torr]	$<10^{-6}$ [10^{-6}]	0	agree
144	$<2.6 \times 10^{-5}$ Pa [10^{-6} torr]	$<10^{-7}$ [10^{-6}]	0	agree
148	nd	$<10^{-7}$ [10^{-6}]	-	-
151	2.47 Pa (extrapol.) 1.85×10^{-2} torr	$<10^{-7}$ [10^{-6}]	-4.3	disagree

Chem. No.	MPD vapour pressure	SAR vapour pressure [torr]	Difference [± log units]	Result
155	2.4 x 10^{-8} kPa [10^{-6} torr]	< 10^{-6} [10^{-6}]	0	agree
156	0.07 Pa 5.25 x 10^{-4} torr	0.054	+2.0	disagree
164	220 Pa 1.65 torr	< 10^{-5}	-5.2	disagree
170	1.88 x 10^{-6} kPa 1.41 x 10^{-5} torr	< 10^{-5}	-0.1	agree
173	2.1 Pa 1.57 x 10^{-2} torr	≤ 10^{-6} [10^{-6}]	-4.2	disagree
176	9.6 x 10^{-11} Pa [10^{-6} torr]	< 10^{-12} [10^{-6}]	0	agree
182	747 Pa (extrapol.) 5.6 torr	10^{-6}	-6.7	disagree
186	8.9 x 10^{-10} kPa [10^{-6} torr]	10^{-8} [10^{-6}]	0	agree
192	0.0085 kPa 6.37 x 10^{-2} torr	0.5	+0.9	agree
194	nd	< 10^{-5}	-	-
196	nd	< 10^{-8}	-	-
197	8.82 x 10^{-5} Pa [10^{-6} torr]	< 10^{-6} [10^{-6}]	0	agree
200	4 Pa 3.0 x 10^{-2} torr	3 x 10^{-4}	-2.0	disagree

Chem. No.	MPD vapour pressure	SAR vapour pressure [torr]	Difference [± log units]	Result
204	1.1 x 10^{-7} Pa [10^{-6} torr]	10^{-7} [10^{-6}]	0	agree
214	0.6 x 10^{-4} Pa [10^{-6} torr]	$<10^{-6}$ [10^{-6}]	0	agree
216	1 x 10^{-8} kPa [10^{-6} torr]	4.7 x 10^{-8} [10^{-6}]	0	agree
217	nd	$<10^{-7}$	-	-
218	10.2 x 10^{-3} Pa 7.65 x 10^{-5} torr	<0.01	+2.1	disagree
219	0.0067 mbar 5.02 x 10^{-3} torr	0.008	+0.2	agree
222	1.34 Pa 1 x 10^{-2} torr	0.016	+0.2	agree
224	nd	$<10^{-6}$	-	-
235	2.1 x 10^{-3} Pa 1.57 x 10^{-5} torr	$\leq 10^{-6}$ [10^{-6}]	-1.2	disagree
237	0.31 kPa 2.32 torr	10^{-6}	0	agree
239	2.54 x 10^{-15} Pa [10^{-6}]	10^{-6}	0	agree
240	nd	«10^{-6} [10^{-6}]	-	-
241	2.0 x 10^{-4} 1.6 x 10^{-6} torr	10^{-5}	-0.2	agree

Chem. No.	MPD vapour pressure	SAR vapour pressure [torr]	Difference [± log units]	Result
242	0.90 Pa 6.6×10^{-3} torr	10^{-5}	-2.8	disagree
253	2×10^{-5} Pa [10^{-6}]	$\leq 1.5 \times 10^{-7}$ [10^{-6}]	0	agree
256	1.0 Pa 7.5×10^{-3} torr	10^{-4}	-1.9	disagree
263	nd	$< 10^{-8}$ [10^{-6}]	-	-
265	nd	$< 10^{-5}$	-	-
267	nd	$< 10^{-8}$ [10^{-6}]	-	-
268	4.9 Pa 3.67×10^{-2} torr	1.3×10^{-3}	-1.4	disagree
269	2×10^{-3} torr	2×10^{-3}	0	agree
270	1.3×10^{-5} Pa [10^{-6} torr]	5×10^{-8} [10^{-6}]	0	agree
271	<0.01 kPa 7.5×10^{-2} torr	$< 10^{-7}$ [10^{-6}]	-4.8	disagree
275	5.4×10^{-9} Pa [10^{-6} torr]	$< 10^{-7}$ [10^{-6}]	0	agree
278	6.06×10^{-3} Pa 4.54×10^{-5} torr	4.1×10^{-6}	-1.0	agree
281	4.3×10^{-2} Pa 3.22×10^{-4} torr	7.5×10^{-4}	+0.3	agree

Chem. No.	MPD vapour pressure	SAR vapour pressure [torr]	Difference [± log units]	Result
283/ 429	4.5 Pa 3.37×10^{-2} torr	0.3	+0.9	agree
286	6.4 Pa (extrapol.) 4.8×10^{-2} torr	$<10^{-8}$ [10^{-6}]	-4.7	disagree
287	0.9 Pa (extrapol.) 6.7×10^{-3} torr	$<10^{-7}$ [10^{-6}]	-3.8	disagree
289	$<4.9 \times 10^{-8}$ Pa [10^{-6} torr]	$<10^{-9}$ [10^{-6}]	0	agree
291	nd	$<10^{-7}$ [10^{-6}]	-	-
292	1.55 Pa 1.16×10^{-2} torr	2.9×10^{-7} [10^{-6}]	-4.0	disagree
300	1.7×10^{-2} (1.27×10^{-4} torr)	2.5×10^{-4}	+0.3	agree
307	nd	$<10^{-3}$	-	-
309	8×10^{-4} Pa 6×10^{-6} torr	$<10^{-6}$ [10^{-6}]	-0.7	agree
312	96.5 Pa 0.724 torr	$<10^{-7}$ [10^{-6}]	-5.8	disagree
318	nd	$<10^{-8}$ [10^{-6}]	-	-
320	nd	$<10^{-8}$ [10^{-6}]	-	-
321	2.9×10^{-7} Pa [10^{-6} torr]	$<10^{-5}$	+1.0	agree

Chem. No.	MPD vapour pressure	SAR vapour pressure [torr]	Difference [± log units]	Result
330	10^{-6} Pa [10^{-6} torr]	$< 10^{-6}$ [10^{-6}]	0	agree
335	1.5 Pa 1.13×10^{-2} torr	$< 10^{-8}$ [10^{-6}]	-4.0	disagree
336	nd	$< 10^{-8}$ [10^{-6}]	-	-
337	3.67×10^{-4} Pa 2.75×10^{-6} torr	4×10^{-4}	+2.1	disagree
340	nd	$< 10^{-3}$	-	-
341	nd	$< 10^{-8}$ [10^{-6}]	-	-
342	7.3 Pa [5.5 torr]	0.1	-1.7	disagree
344	nd	10^{-4}	-	-
348	≤0.2 Pa 1.5×10^{-3} torr	10^{-9} [10^{-6}]	-3.2	disagree
349	nd	$< 10^{-8}$ [10^{-6}]	-	-
354	2.2×10^{-4} Pa 1.65×10^{-6} torr	$< 10^{-5}$	+0.8	agree
355	3.02×10^{-6} Pa 2.2×10^{-6} torr	$< 10^{-6}$ [10^{-6}]	-0.3	agree
360	1.8×10^{-4} Pa 1.35×10^{-6} torr	$< 10^{-7}$ [10^{-6}]	-0.1	agree

Chem. No.	MPD vapour pressure	SAR vapour pressure [torr]	Difference [± log units]	Result
361	$<10^{-7}$ [10^{-6} torr]	10^{-7} [10^{-6}]	0	agree
362	1.7×10^{-4} at 84°C [10^{-6} torr/rt]	$<10^{-6}$ [10^{-6}]	0	agree
364	nd	$\leq 10^{-6}$	-	-
366	10^{-8} at 100°C [10^{-6} torr]	$<10^{-6}$ [10^{-6}]	0	agree
368	0.075 kPa 0.56 torr	1.5	+0.4	agree
369	0.01 kPa 7.5×10^{-2} torr	$<10^{-6}$ [10^{-6}]	-4.9	agree
370	153.3 [1.15 torr]	4.1	+0.6	agree
373	558 Pa 4.18 torr	2	-0.3	agree
376	65 Pa 0.487 torr	$<10^{-8}$ [10^{-6}]	-5.7	disagree
379	1140 Pa 8.55 torr	8.5	0	agree
381	«10^{-8} [10^{-6} torr]	$<10^{-7}$ [10^{-6}]	0	agree
383	5×10^{-15} Pa [10^{-6} torr]	$<10^{-6}$ [10^{-6}]	0	agree
386	1.0×10^{-6} Pa / 9.7×10^{-7} Pa [10^{-6} torr]	$<10^{-7}$ [10^{-6}]	0	agree

Chem. No.	MPD vapour pressure	SAR vapour pressure [torr]	Difference [± log units]	Result
393	«10^{-8} kPa [10^{-6}]	< 10^{-8} [10^{-6}]	0	agree
394	2.6 x 10^{-5} Pa [10^{-6} torr]	< 10^{-6} [10^{-6}]	0	agree
396	33 Pa 0.247 torr	< 10^{-8} [10^{-6}]	-5.4	disagree
398	6.8 Pa (40°C) 0.02 torr (rt)	0.04	+0.3	agree
401	<10Pa 7.5 x 10^{-2} torr	< 10^{-10} [10^{-6}]	-4.8	disagree
406	<2.5 x 10^{-2} 1.87 x 10^{-4} torr	< 10^{-8} [10^{-6}]	-2.3	disagree
411	«10^{-8} kPa [10^{-6} torr]	< 10^{-6} [10^{-6}]	0	agree
413	2.3 x 10^{-4} Pa 1.72 x 10^{-6} torr	< 10^{-6} [10^{-6}]	-0.2	agree
414	5.21 x 10^{-4} Pa 3.91 x 10^{-6} torr	[10^{-6}]	-0.6	agree
415	0.04 Pa 3 x 10^{-6} torr	[10^{-6}]	-2.5	disagree
416	<0.1Pa 7.5 x 10^{-4} torr	< 10^{-6} [10^{-6}]	-2.8	disagree
417	2.5 x 10^{-2} Pa 1.87 x 10^{-4} torr	< 10^{-7} [10^{-6}]	-3.2	disagree
420	9.01 x 10^{-6} Pa [10^{-6} torr]	3.4 x 10^{-4}	+1.7	disagree

Chem. No.	MPD vapour pressure	SAR vapour pressure [torr]	Difference [± log units]	Result
421	1 Pa 7.5×10^{-3} torr	$<10^{-6}$ [10^{-6}]	-3.8	disagree
425	<10 Pa <0.075 torr	0.03	-0.4	agree
431	$\leq 1.6 \times 10^{-8}$ Pa [10^{-6} torr]	$<10^{-6}$ [10^{-6}]	0	agree
436	3.1×10^{-2} Pa 2.33×10^{-4} torr	$<10^{-7}$ [10^{-6}]	-2.3	disagree
437	9600 Pa 72 torr	$<10^{-4}$	-5.8	disagree
439	$\leq 7.1 \times 10^{-16}$ Pa [10^{-6} torr]	$<10^{-8}$ [10^{-6}]	0	agree
441	nd	$<10^{-6}$	-	-
442	3.2×10^{-8} Pa [10^{-6} torr]	$<10^{-3}$	+3.0	disagree
443	1.08 kPa 8.1 torr	11.4	+0.1	agree
444	2.3×10^{-3} Pa 1.72×10^{-5} torr	0.07	+3.6	disagree
445	nd	$<10^{-6}$ [10^{-6}]	-	-
446	2.4×10^{-7} Pa [10^{-6} torr]	$<10^{-7}$ [10^{-6}]	0	agree
451	0.05 Pa 3.75×10^{-4} torr	≤0.01	+1.4	disagree
472	350 Pa (extrapol.) 2.63 torr	3×10^{-4}	-3.9	disagree

WATER SOLUBILITY: COMPARISON OF TEST RESULTS AND PREDICTIONS

Chem. No.	MPD water sol. [mg/l]	SAR water sol. [mg/l]	Difference [± log units]	Result
4	reacts (decomposes)	reacts	-	agree
6	hydrophobic	$< 10^{-3}$	-	agree
16	>700,000 [10,000]	>700,000 [10,000]	0	agree
17	100,000 [10,000]	50,000 [10,000]	0	agree
21	<0.8	<0.01	-1.9	disagree
23	mixes with each other in all ratios	~200,000	-	agree
24	17.2	$\leq 0.15 \times 10^{-3}$ [0.01]	-3.2	disagree
26	0.1 - 0.5	$< 1.6 \times 10^{-3}$ [0.01]	-1.7	disagree
37	1	1	0	agree
44	<5	0.01	-2.7	disagree
47	145.7	<1	-2.2	disagree
49	1,450	~100,000 [10,000]	0.8	agree
50	5.3 +/-3	<0.1	-1.4	disagree

Chem. No.	MPD water sol. [mg/l]	SAR water sol. [mg/l]	Difference [± log units]	Result
53	-- nd	≤0.1	-	-
54	17.9	500	+1.4	disagree
61	<0.05	<0.1	+0.3	agree
68	145,000 [10,000]	>100,000 [10,000]	0	agree
69	>48,000 [10,000]	200,000 [10,000]	0	agree
70	30	<2	-1.1	disagree
76	7.7	<10	+ 0.1	agree
78	<0.05	<1	+ 1.3	disagree
79	<0.03	<0.1	+ 1.5	disagree
87	4,040	2,000	-0.3	agree
96	<500,000 [10,000]	100,000 [10,000]	0	agree
99	reacts	reacts	-	agree
101	32,000 [10,000]	<250,000 [10,000]	0	agree

Chem. No.	MPD water sol. [mg/l]	SAR water sol. [mg/l]	Difference [± log units]	Result
102	0.17	<1	+0.7	agree
106	<0.2	$2.4.10^{-3}$ [0.01]	-1.3	disagree
107	reacts	reacts	-	agree
108	0.19	≤0.1	-0.3	agree
110	<1	0.01	-2.0	disagree
113	0.065	5×10^{-3} [0.01]	-0.15	agree
118	58	<25,000 [10,000]	+2.2	disagree
124	182	900	+0.7	agree
128	<10	<1	-1.0	agree
133	2.3	2.3	0	agree
144	<0.01	<1	+2.0	disagree
148	<0.005 [0.01]	<0.1	+1.0	agree
151	5.61	0.1 - 10	-0.7	agree

Chem. No.	MPD water sol. [mg/l]	SAR water sol. [mg/l]	Difference [± log units]	Result
155	<0.3	$\leq 10^{-4}$	-1.4	disagree
156	13	10 - 100	+0.5	agree
164	39	<5	-0.9	agree
170	69,190 [10,000]	140,000 [10,000]	0	agree
173	nd	≤5	-	-
176	<10	<10	0	agree
182	<10	<2,000	+2.3	disagree
186	0.9	9	+1.0	agree
192	hydrolyses	2,500	-	-
194	479,000 [10,000]	≥100,000 [10,000]	0	agree
196	>300,000 [10,000]	>200,000 [10,000]	0	agree
197	8.2	<1000	+2.1	disagree
200	0.071	0.0064 [0.01]	-0.8	agree

Chem. No.	MPD water sol. [mg/l]	SAR water sol. [mg/l]	Difference [± log units]	Result
204	0.27	<0.1	-0.4	agree
214	<0.1	<1000	+4.0	disagree
216	4.2×10^3	<100	-1.6	disagree
217	<0.07	<100	+3.1	disagree
218	63+/-5	<50	-0.1	agree
219	363	<1000	+0.4	agree
222	1.52	reacts	-	-
224	180,000 [10,000]	60,000 [10,000]	0	agree
235	<10 (hydrolyses)	≤0.1	-2.0	agree
237	18	18 (reacts)	0	agree
239	<0.01	$\leq 10^{-3}$ [0.01]	0	agree
240	299,000 [10,000]	100,000-200,000 [10,000]	0	agree
241	4.55×10^6 [10,000]	>100,000 [10,000]	0	agree

Chem. No.	MPD water sol. [mg/l]	SAR water sol. [mg/l]	Difference [± log units]	Result
242	$>11.7 \times 10^6$ [10,000]	100,000 [10,000]	0	agree
253	<0.02	0.02	0	agree
256	470,000 [10,000]	10,000 - 50,000 [10,000]	0	agree
263	77,500 [10,000]	90,000 - 100,000 [10,000]	0	agree
265	712,900 [10,000]	1,000 - 5,000	-0.6	agree
267	nd	<0.1	-	-
268	2.3	<5	+0.3	agree
269	3	3	0	agree
270	730	1 - 1000	-	-
271	5,000 - 10,000	<1000	-0.9	agree
275	<0.04	0.2	+0.7	agree
278	<30	≤10	-0.4	agree
281	3	<10	+0.4	agree

Chem. No.	MPD water sol. [mg/l]	SAR water sol. [mg/l]	Difference [± log units]	Result
283/ 429	<0.5	$\leq 10^{-3}$ [0.01]	-1.7	disagree
286	0.019	$< 10^{-3}$ [0.01]	-0.3	agree
287	0.005 - 0.009 [0.01]	<0.1	+1.0	agree
289	0.091	≤0.01	+0.04	agree
291	<60	<1	-1.8	agree
292	37	900 (pH 1.1) 45 (pH 7.8) (Lit. value)	-	-
300	56	<1000	+1.2	disagree
307	16	<1000	+1.8	disagree
309	0.022 - 0.042	<1	+1.5	disagree
312	214,000 [10,000]	>100,000 [10,000]	0	agree
318	53	<100	+0.3	agree
320	<0.007 [0.01]	<10	+3.0	disagree
321	57,000 [10,000]	5,000 - 15,000	0	agree

Chem. No.	MPD water sol. [mg/l]	SAR water sol. [mg/l]	Difference [± log units]	Result
330	1570	>100,000 [10,000]	0.8	agree
335	n.d.	<10	-	-
336	11,500 [10,000]	<100	-2.0	disagree
337	660	<7	-2.0	disagree
340	749	20,000 [10,000]	+1.1	disagree
341	66	1,000 - 10,000	+1.9	disagree
342	65,800	80,000	+0.08	agree
344	nd (subst. only stable in aqu. solution)	200,000	-	-
348	0.053	<0.1	+0.3	agree
349	<0.2	<0.1	-0.3	agree
354	31	<50	+0.2	agree
355	0.008 [0.01]	7.9×10^{-3} [0.01]	0	agree
360	1410	500 - 1,500	-0.1	agree

Chem. No.	MPD water sol. [mg/l]	SAR water sol. [mg/l]	Difference [± log units]	Result
361	0.153	<10	+1.8	disagree
362	4.6 - 4.9	<150	+1.5	disagree
364	>300,000 [10,000]	≥200,000 [10,000]	0	agree
366	11	«0.1	-2.0	disagree
368	14	reacts	-	-
369	479,000 [10,000]	370,000 [10,000]	0	agree
370	nd (decomposes)	8,000	-	-
373	12.7	5 - 15	-0.1	agree
376	0.04	0.03	-0.1	agree
379	1.45	9	+0.8	agree
381	$<10^{-3}$ [0.01]	<0.01	0	agree
383	<0.03	«0.1	+0.5	agree
386	19 pH 5 18 pH 7 16 pH 9	<300	+1.2	disagree

Chem. No.	MPD water sol. [mg/l]	SAR water sol. [mg/l]	Difference [± log units]	Result
393	0.6	<10	+1.2	disagree
394	1140 x 10^3 [10,000]	»500,000 [10,000]	-0	agree
396	61,400 [10,000]	1,000 - 2,000	-0.8	agree
398	hydrolyses	reacts	-	agree
401	137.5	500 - 1,000	0.7	agree
406	<0.01	0.1	+1	agree
411	<0.0015 [0.01]	≤0.1	+1	agree
413	<0.03	1	+1.5	disagree
414	3,300	100 - 10,000	-0.5	agree
415	≤0.005 [0.01]	<0.1	+1.0	agree
416	0.0048 [0.01]	<0.1	+1.0	agree
417	1.26 x 10^{-4} [0.01]	<1	+2.0	disagree
420	1.6 pH 5 1.4 pH 7 1.5 pH 9	<10	+0.8	agree

Chem. No.	MPD water sol. [mg/l]	SAR water sol. [mg/l]	Difference [± log units]	Result
421	50×10^{-6} [0.01]	<1	+2.0	disagree
425	>990,000 [10,000]	200,000 [10,000]	0	agree
431	0.078	<0.1	+0.1	agree
436	$<10^{6}$	<100	-2.0	disagree
437	0.012	<1	+1.9	disagree
439	480	5,000 - 50,000	+1.3	disagree
441	9,550	≥40,000 [10,000]	+0.02	disagree
442	6,210	≤ 10,000	+0.2	agree
443	nd	1,000 - 10,000	-	-
444	61	100	+0.2	agree
445	<0.5	<1 (acid)	+0.3	agree
446	<0.02	<0.001 [0.01]	-0.3	agree
451	20,000 [10,000]	10,000 - 50,000 [10,000]	0	agree
472	16.2	<0.05	-2.5	disagree

PARTITION COEFFICIENT: **COMPARISON OF TEST RESULTS AND PREDICTIONS**

Chem. No.	MPD $\log P_{ow}$	SAR $\log P_{ow}$	Difference [± log units]	Result
4	nd	nd	-	-
6	nd	nd	-	-
16	0.014	<-2.5	-2.5	disagree
17	nd	nd	-	-
21	>4.15	>6	+1.85	disagree
23	-4.68	nd	-	-
24	4.28	6.9	[+1.72]	disagree
26	4.74	>6 (10.8)	[+1.26]	disagree
37	∞	2.5	-	-
44	3.0	nd	-	-
47	3.93	5.3	+1.37	disagree
49	1.65	≥6	+4.35	disagree
50	1.3	nd	-	-

Chem. No.	MPD log P_{ow}	SAR log P_{ow}	Difference [± log units]	Result
53	nd	>6	-	-
54	3.09	2.71	-0.38	agree
61	4.38	>6 (9.2)	[+1.62]	disagree
68	nd	<-2.5	-	-
69	nd	<-2.5	-	-
70	4.4	>6	+1.6	disagree
76	nd	nd	-	-
78	nd	5.9	-	-
79	nd	nd	-	-
87	2.02	2.1	+0.08	agree
96	nd	<-2.5	-	-
99	nd	nd	-	-
101	nd	nd	-	-

Chem. No.	MPD log P_{ow}	SAR log P_{ow}	Difference [± log units]	Result
102	nd	>6 (14.4)	-	-
106	nd	>6 (6.94)	-	-
107	nd	nd	-	-
108	>5	~5	0	agree
110	nd	>6	-	-
113	4.01	>6 (10.8)	[+1.99]	disagree
118	nd	6.8	-	-
124	2.46	1 - 2	-0.96	agree
128	nd	3.4	-	-
133	3.6	3.6	0	agree
144	5.8	>6 (11.8)	[+0.2]	agree
148	nd	>6	-	-
151	4.87	5.3	+0.43	agree

Chem. No.	MPD $\log P_{ow}$	SAR $\log P_{ow}$	Difference [± log units]	Result
155	nd	>6	-	-
156	4.65	3.7	-0.95	agree
164	3.0	»6	+3	disagree
170	-0.823 to -1.148	0	+0.98	agree
173	1.9/2.0	3.8	+1.85	disagree
176	4.5	≥6	+1.5	disagree
182	5.42	»6 (11.2)	[+0.58]	agree
186	5.6	4	-1.6	disagree
192	0.74	<3.8	+3.06	disagree
194	nd	3.6	-	-
196	nd	-1.8	-	-
197	3.6	1.8	-1.8	disagree
200	6.25	>6 (6.7)	[0]	agree

Chem. No.	MPD log P_{ow}	SAR log P_{ow}	Difference [± log units]	Result
204	3.89	>6	+2.11	disagree
214	nd	>6	-	-
216	nd	nd	-	-
217	nd	2.5	-	-
218	3.84	4.1	+0.26	agree
219	1.65	2.3	+0.65	agree
222	nd	reacts	-	-
224	nd	nd	-	-
235	nd	>6	-	-
237	5.1	nd	-	-
239	>3.29	>6 (12.9)	[2.71]	disagree
240	nd	nd	-	-
241	-2.76	[0]	0	agree

Chem. No.	MPD log P_{ow}	SAR log P_{ow}	Difference [± log units]	Result
242	-2.4	<0	[0]	agree
253	nd	>6 (10.5)	-	-
256	-1.3	<-2.5	[0]	agree
263	-2.36	<0	[0]	agree
265	<-2.5	≤-1.075	[0]	agree
267	nd	nd	-	-
268	4.6	≥5.4	+0.8	agree
269	4.53	5.0	+0.47	agree
270	-1.1 (pH 7.65) +0.55 (pH 8.72)	3	>1	disagree
271	nd	~5	-	-
275	nd	4.3	-	-
278	3.95	5.2	+1.25	disagree
281	4.41	5.2	+0.79	agree

Chem. No.	MPD log P_{ow}	SAR log P_{ow}	Difference [± log units]	Result
283/ 429	nd	nd	-	-
286	≥6	>6	0	agree
287	≥5	»6	1	agree
289	nd	5.5	-	-
291	nd	>6	-	-
292	2.88	3.4	+0.52	agree
300	3.67	4.2	+0.53	agree
307	3.07	3.1	-0.03	agree
309	3.9	>6	+2.1	disagree
312	1.09	<0	-1.09	disagree
318	nd	3 - 4	-	-
320	nd	nd	-	-
321	1.11 (pH 2)	-0.25 (missing fragment)	-1.36	disagree

Chem. No.	MPD log P_{ow}	SAR log P_{ow}	Difference [± log units]	Result
330	<-3	-0.85	[0]	agree
335	~3	nd	-	-
336	<-1	nd	-	-
337	3.05	1.7 - 1.9	-1.15	disagree
340	0.492	~0	-0.49	agree
341	nd	<-2.5	-	-
342	-0.0053	0.55	0.55	agree
344	nd	<-2.5	-	-
348	5.9	>6 (11.5)	[+0.1]	agree
349	>7.24	>6	[0]	agree
354	2.89	3.3	+0.41	agree
355	1.92	>6 (8.0)	+4.08	disagree
360	1.04	3.2	+2.16	disagree

Chem. No.	MPD log P_{ow}	SAR log P_{ow}	Difference [± log units]	Result
361	4.85	»6 (>8)	[+1.15]	disagree
362	2.3	3.0	+0.7	agree
364	nd	<-2.5	-	-
366	3.7	nd	-	-
368	4.3	3.1	-1.2	disagree
369	<-2.5	nd	-	-
370	nd	4.9	-	-
373	4.18	4.4	+0.22	agree
376	>5.7	>6 (11.6)	[+0.3]	agree
379	4.74	4.2	-0.54	agree
381	nd	nd	-	-
383	nd	>6	-	-
386	2.62 / 2.73	3	0.38	agree

Chem. No.	MPD log P_{ow}	SAR log P_{ow}	Difference [± log units]	Result
393	nd	3.6	-	-
394	-2.46	<-2.5	[0]	agree
396	-1.47	-2.4	[0]	agree
398	>2.7	3.3	+0.6	agree
401	-3.27 / 0.758	nd	-	-
406	4.65	5.3	+0.65	agree
411	nd	>6	-	-
413	nd	>6	-	-
414	0.258	2 - 3.5	+2.5	disagree
415	7	>6	[0]	agree
416	nd	»6	-	-
417	5.1	5.4	+0.3	agree
420	3.38	3.8	+0.42	agree

Chem. No.	MPD log P_{ow}	SAR log P_{ow}	Difference [± log units]	Result
421	≥5	5.6	+0.6	agree
425	nd	0.31	-	-
431	4.7	»6 (12.0)	> +1.3	disagree
436	nd	3.5 - 4.6	-	-
437	6.4	»6 (9)	[0]	agree
439	-1.98	2	+3.98	disagree
441	1.37	2.18	+0.81	agree
442	-1.88	≤-2.5	[0]	agree
443	1.96	1.16	-0.8	agree
444	3.39	3.68	+0.29	agree
445	nd	nd	-	-
446	nd	>6	-	-
451	2.63	0.99	1.64	disagree
472	>4.6	>6 (6.78)	+1.4	disagree

BIODEGRADATION: COMPARISON OF TEST RESULTS AND PREDICTIONS

Chem. No.	MPD data [% Biodegradation]	SAR data	Result
4	nd (reacts)	reacts	-
6	nd	weeks	-
16	nd (BOD/COD = 0.75)	days	-
17	nd (BOD/COD = 0.23)	months or longer (persistent)	-
21	0%	months	agree
23	35% (adsorption)	months	-
24	0%	weeks to months	agree
26	7%	months or longer (persistent)	agree
37	34%	weeks	agree
44	6%	months or longer (persistent)	agree
47	0%	weeks	agree
49	40%	weeks to months	agree
50	2%	months or longer (persistent)	agree

Chem. No.	MPD data [% Biodegradation]	SAR data	Result
53	nd	months or longer (persistent)	-
54	1%	weeks to months	agree
61	1.5%	months	agree
68	10%	months or longer (persistent)	agree
69	~10%	months or longer (persistent)	agree
70	0%	months or longer (persistent)	agree
76	12%	months or more	agree
78	nd (insoluble) (BOD/COD = 0.01)	months or longer (persistent)	-
79	nd (insoluble) DOB/COD = 0.03	nd (insoluble)	-
87	100%	days to weeks	agree
96	10%	months or longer (persistent)	agree
99	82%	nd	-
101	10%	months or longer (persistent)	agree

Chem. No.	MPD data [% Biodegradation]	SAR data	Result
102	4%	months or longer (persistent)	agree
106	5%	months or longer (persistent)	agree
107	nd (flammable in air, decomp with water	reaction with O_2 and H_2O	-
108	3%	months or longer (persistent)	agree
110	73%	days to weeks	agree
113	nd (BOD/COD = 0.23)	weeks to months	-
118	5%	weeks to months	agree
124	0%	nd (probably slow)	-
128	4%	months	agree
133	10%	months or longer (persistent)	agree
144	0%	weeks to months	agree
148	0%	months or longer (persistent)	agree
151	4%	weeks	agree

Chem. No.	MPD data [% Biodegradation]	SAR data	Result
155	13%	weeks to months	agree
156	81%	weeks	disagree
164	0%	months or longer (persistent)	agree
170	27%	weeks	agree
173	21%	nd	-
176	6%	months or longer (persistent)	agree
182	11%	weeks	agree
186	0%	months or longer (persistent)	agree
192	>80%	days to weeks	agree
194	nd	months	-
196	0%	months	agree
197	0%	months or longer (persistent)	agree
200	0%	weeks to months	agree

Chem. No.	MPD data [% Biodegradation]	SAR data	Result
204	0%	months or longer (persistent)	agree
214	20%	weeks	agree
216	26%	nd	-
217	12%	months or longer (persistent)	agree
218	1%	weeks to months	agree
219	0%	weeks	agree
222	0%	months	agree
224	10%	months or longer (persistent)	agree
235	7%	weeks to months	agree
237	0%	nd	-
239	21%	months or longer (persistent)	agree
240	20%	months or longer (persistent)	agree
241	5%	weeks	agree

Chem. No.	MPD data [% Biodegradation]	SAR data	Result
242	0%	weeks	agree
253	4%	months	agree
256	46%	days to weeks	disagree
263	0%	months or longer (persistent)	agree
265	81%	nd	-
267	nd (insoluble)	months or longer (persistent)	-
268	70%	months or longer (persistent)	disagree
269	2%	months	agree
270	16%	weeks to months	agree
271	33%	weeks to months	agree
275	0%	months or longer (persistent)	agree
278	80%	days to weeks	agree
281	1%	nd	-

Chem. No.	MPD data [% Biodegradation]	SAR data	Result
283/ 429	nd	months or longer (persistent)	-
286	3%	months	agree
287	2%	months or longer (persistent)	agree
289	3%	months or longer (persistent)	agree
291	6%	months or longer (persistent)	agree
292	0%	months or longer (persistent)	agree
300	2%	months or longer (persistent)	agree
307	0%	months	agree
309	6%	months or longer (persistent)	agree
312	13%	weeks	agree
318	35%	months or longer (persistent)	agree
320	nd	months or longer (persistent)	-
321	34%	weeks to months	agree

Chem. No.	MPD Data [% Biodegradation]	SAR Biodegradation Data	Result
330	21%	weeks to months	agree
335	14%	months or longer (persistent)	agree
336	10%	weeks	agree
337	0%	weeks	agree
340	5%	weeks	agree
341	30%	weeks to months	agree
342	62%	months	disagree
344	0%	weeks	agree
348	2.5%	months	agree
349	nd	months or longer (persistent)	-
354	5%	weeks	agree
355	48%	months	agree
360	8%	weeks	agree

Chem. No.	MPD data [% Biodegradation]	SAR data	Result
361	0%	months or longer (persistent)	agree
362	8%	weeks to months	agree
364	0%	months or longer (persistent)	agree
366	0%	months or longer (persistent)	agree
368	7%	nd	-
369	19%	weeks to months	agree
370	nd (reacts with water)	months or longer (persistent)	-
373	20%	weeks	agree
376	nd (insoluble)	weeks to months	-
379	3%	nd	-
381	10%	months or longer (persistent)	agree
383	11%	months or longer (persistent)	agree
386	0%	months	agree

hem. No.	MPD data [% Biodegradation]	SAR data	Result
393	30%	months or longer (persistent)	agree
394	0%	months	agree
396	10%	nd	-
398	100%	nd	-
401	45%	weeks to months	agree
406	4%	months or longer (persistent)	agree
411	20%	months or longer (persistent)	agree
413	74%	weeks to months	disagree
414	27%	weeks to months	agree
415	8%	months or longer (persistent)	agree
416	4%	months or longer (persistent)	agree
417	15%	months or longer (persistent)	agree
420	3%	weeks	agree

Chem. No.	MPD data [% Biodegradation]	SAR data	Result
421	18%	weeks	agree
425	30%	days to weeks	disagree
431	21%	weeks	agree
436	0%	days to weeks	disagree
437	10.5%	months	agree
439	0%	months or longer (persistent)	agree
441	<3%	weeks to months	agree
442	0%	weeks	agree
443	20%	weeks	agree
444	33%	weeks	agree
445	nd (polymer)	months or longer (persistent)	-
446	10%	months	agree
451	20%	days to weeks	disagree
472	100%	days to weeks	agree

TOXICITY TO FISH: COMPARISON OF TEST RESULTS AND PREDICTIONS

Chem. No.	MPD LC50 value [mg/l]	SAR LC50 value [mg/l]	Difference [± log units]	Result
4	nd	>100	-	-
6	>500	>11	-1.7	disagree
16	>1000	>100	[0]	agree
17	5.1	>0.5	-1.05	disagree
21	nd	NTS	-	-
23	>2100	>100	[0]	agree
24	1.8	0.05	-1.52	disagree
26	NTS	NTS	-	agree
37	>2	8.8	0.64	agree
44	nd	NTS	-	-
47	1.8 - 3.2	≤0.32	-	-
49	11	30	0.43	agree
50	NTS	NTS	-	agree

Chem. No.	MPD LC50 value [mg/l]	SAR LC50 value [mg/l]	Difference [± log units]	Result
53	2.0	0.1	-1.30	disagree
54	9.0	27.0	0.48	agree
61	NTS	NTS	-	agree
68	>500	>100	[0]	agree
69	>500	>100	[0]	agree
70	NTS	NTS	-	agree
76	2.8	NTS	-	disagree
78	172.0	0.3	-2.70	disagree
79	>1000	NTS	-	agree
87	8.5	21.0	-0.40	agree
96	>500	>100	[0]	agree
99	>60	>100	0.23	agree
101	>500	>100	[0]	agree

Chem. No.	MPD LC50 value [mg/l]	SAR LC50 value [mg/l]	Difference [± log units]	Result
102	NTS >74	NTS	-	agree
106	118	NTS	-	agree
107	nd	NTS	-	-
108	0.1	0.35	0.54	agree
110	NTS	NTS	-	agree
113	>1000	NTS	-	agree
118	1.1	0.07	-1.22	disagree
124	16.9	1.4	-1.10	disagree
128	>100	13.0	-0.89	agree
133	10 - 100	<10.2	-	-
144	NTS >100	NTS	-	agree
148	NTS >500	NTS	-	agree
151	0.32	0.42	0.13	agree

Chem. No.	MPD LC50 value [mg/l]	SAR LC50 value [mg/l]	Difference [± log units]	Result
155	NTS >100	NTS	-	agree
156	4.7	1.37	-0.54	agree
164	NTS >40	NTS	-	agree
170	9.0	7.1	-0.10	agree
173	1.5	≥8.4	0.75	agree
176	7.3	NTS	-	disagree
182	2.2	NTS	-	disagree
186	0.43	>0.1	-0.64	agree
192	71	≤16	-	-
194	10 - 100	≤10.2	-	-
196	>1000	>100	[0]	agree
197	0.46	0.60	0.11	agree
200	NTS >0.7	NTS	-	agree

Chem. No.	MPD LC50 value [mg/l]	SAR LC50 value [mg/l]	Difference [± log units]	Result
204	NTS >0.3	NTS	-	agree
214	111.8	0.38	-2.52	disagree
216	>100	NTS	-	agree
217	220	>100	[0]	agree
218	6.6	3.8	-0.24	agree
219	17.7	9.0	-0.30	agree
222	0.83	10.0	1.08	disagree
224	>100	121.0	[0]	agree
235	0.76	0.40	0.26	agree
237	244	>100	[0]	agree
239	NTS	NTS	-	agree
240	>500	>100	[0]	agree
241	1000	>100	[0]	agree

Chem. No.	MPD LC50 value [mg/l]	SAR LC50 value [mg/l]	Difference [± log units]	Result
242	874	>100	[0]	agree
253	NTS >100	NTS	-	agree
256	>1000	1700	[0]	agree
263	53	7	-0.89	agree
265	>1000	>1000	0	agree
267	nd	NTS	-	-
268	>500	1.0	-2.70	disagree
269	NTS	NTS	-	agree
270	>51	21	-0.40	agree
271	47	100	0.32	agree
275	83	0.24	-2.52	disagree
278	8.5	11	0.11	agree
281	1.03	NTS	-	disagree

Chem. No.	MPD LC50 value [mg/l]	SAR LC50 value [mg/l]	Difference [± log units]	Result
283/ 429	NTS >500	NTS	-	agree
286	NTS >100	NTS	-	agree
287	NTS >1000	NTS	-	agree
289	NTS >1000	NTS	-	agree
291	NTS >100	NTS	-	agree
292	5.7	1.4	-0.60	agree
300	1.7	1.6	-0.03	agree
307	6.9	16.3	0.38	agree
309	NTS	NTS	-	agree
312	101 (89 - 128)	1500	1.17	disagree
318	NTS >500	NTS	-	agree
320	NTS	NTS	-	agree
321	>69	375	0.73	agree

Chem. No.	MPD LC50 value [mg/l]	SAR LC50 value [mg/l]	Difference [± log units]	Result
330	341	> 1000	-	agree
335	2.0	NTS	-	disagree
336	> 100	7	-1.15	disagree
337	36	4	0.96	agree
340	152	≤1000	-	-
341	> 500	> 1000	-	agree
342	480	> 1000	-	agree
344	> 1000	> 1000	-	agree
348	NTS > 10	NTS	-	agree
349	NTS > 500	NTS	-	agree
354	8.3	≤13.5	-	-
355	NTS	NTS	-	agree
360	> 100	60	-0.22	agree

Chem. No.	MPD LC50 value [mg/l]	SAR LC50 value [mg/l]	Difference [± log units]	Result
361	NTS >1000	NTS	-	agree
362	>1.0	14	1.15	disagree
364	17.8	>100	0.75	agree
366	NTS >135	NTS	-	agree
368	5	>14.8	0.47	agree
369	1671	≥190	[0]	agree
370	114	0.9	-2.10	disagree
373	>100	1.5	-1.82	disagre
376	NTS >100	NTS	-	agree
379	0.72	1.5	0.32	agree
381	NTS >500	NTS	-	agree
383	NTS >67	NTS	-	agree
386	3.4	≤35.3	-	-

Chem. No.	MPD LC50 value [mg/l]	SAR LC50 value [mg/l]	Difference [± log units]	Result
393	100	3.8	-1.42	disagree
394	>1000	>100	[0]	agree
396	>1000	>1000	0	agree
398	>100	>11.5	-0.94	agree
401	77	90	0.07	agree
406	NTS	NTS	-	agree
411	NTS >500	NTS	-	agree
413	NTS >100	NTS	-	agree
414	220	≥100	[0]	agree
415	NTS >100	NTS	-	agree
416	NTS	NTS	-	agree
417	NTS >113	NTS	-	agree
420	1.4	5.9	0.62	agree

Chem. No.	MPD LC50 value [mg/l]	SAR LC50 value [mg/l]	Difference [± log units]	Result
421	nd	0.58	-	-
425	1113	500	0	agree
431	NTS >1000	NTS	-	agree
436	2.7	0.52	-0.72	agree
437	NTS 546	NTS	-	agree
439	>258	110	0	agree
441	160	60	-0.43	agree
442	769	≥100	[0]	agree
443	138	99	0.15	agree
444	7.3	4	-0.26	agree
445	>100	>100	0	agree
446	NTS >22	NTS	-	agree
451	21	≤135	-	-
472	NTS >100	NTS	-	agree

TOXICITY TO DAPHNIA: COMPARISON OF TEST RESULTS AND PREDICTIONS

Chem. No.	MPD EC50 value [mg/l]	SAR EC50 value [mg/l]	Difference [± log units]	Result
4	nd	>100	-	-
6	230 (96 hr)	>140	-0.22	agree
16	1100 (48 hr)	>100	[0]	agree
17	1.2 (48 hr)	>0.2	-0.80	agree
21	nd	NTS	-	-
23	680 (24 hr)	>100	[0]	agree
24	10 (24 hr)	<0.73	-	-
26	NTS (24 hr)	NTS	-	agree
37	>2 (24 hr)	10	- 0.70	agree
44	nd	NTS	-	-
47	2.9 (24 hr)	≤0.57	-	-
49	0.84 (48 hr)	≤30	-	-
50	NTS (24 hr)	NTS	-	agree

Chem. No.	MPD EC50 value [mg/l]	SAR EC50 value [mg/l]	Difference [± log units]	Result
53	131.7 (24 hr)	0.1	-3.15	disagree
54	15.3 (24 hr)	2.2	-085	agree
61	NTS (24 hr)	NTS	-	agree
68	20.5 (24 hr)	> 100	0.69	agree
69	395 (24 hr)	> 100	0.60	agree
70	NTS	NTS	-	agree
76	4.0 (48 hr)	NTS	-	disagree
78	990 (24 hr)	0.1	-4	disagree
79	> 1000 (24 hr)	NTS	-	agree
87	25.5 (48 hr)	8.1	-0.49	agree
96	355 (24 hr)	100	-0.55	agree
99	> 56 (48 hr)	≤100	-	-
101	> 1000 (24 hr)	> 100	[0]	agree

Chem. No.	MPD EC50 value [mg/l]	SAR EC50 value [mg/l]	Difference [± log units]	Result
102	47 (24 hr)	NTS	-	disagree
106	5.6 (24 hr)	NTS	-	disagree
107	nd	>100	-	-
108	1.83 (48 hr)	0.46	0.60	agree
110	0.018 - 0.032 (48 hr)	NTS	-	disagree
113	365 (nominal) (24 hr)	NTS	-	agree
118	9.3 (24 hr)	0.01	-4	disagree
124	5.4 (48 hr)	3.4	-0.20	agree
128	>100 (24 hr)	15.4	-0.82	agree
133	5.35 (24 hr)	≤0.93	-	-
144	NTS >5.3 (48 hr)	NTS	-	agree
148	NTS >7.8	NTS	-	agree
151	8.0 (48 hr)	0.36	-1.35	disagree

Chem. No.	MPD EC50 value [mg/l]	SAR EC50 value [mg/l]	Difference [± log units]	Result
155	4.1 (48 hr)	NTS	-	disagree
156	1.3 (48 hr)	0.45	-0.46	agree
164	16 (48 hr)	NTS	-	disagree
170	53 (24 hr)	1.8	-1.52	disagree
173	5 (48 hr)	≥8.4	0.23	agree
176	NTS (24 hr)	NTS	-	agree
182	1.5 (48 hr)	NTS	-	disagree
186	>50	>0.1	-2.70	disagree
192	801 (48 hr)	≤63.0	- -	-
194	1.72 (48 hr)	≤0.93	-	-
196	>1000	>100	[0]	agree
197	0.01 (48 hr)	0.2	1.30	disagree
200	0.046 (48 hr)	NTS	-	disagree

Chem. No.	MPD EC50 value [mg/l]	SAR EC50 value [mg/l]	Difference [± log units]	Result
204	NTS >0.3 (48 hr)	NTS	-	agree
214	220 (24 hr)	2	-2.05	disagree
216	23 (24 hr)	30	0.11	agree
217	>100 (24 hr)	230	0.36	agree
218	7.2 (48 hr)	1.9	-0.59	agree
219	39.2 (24 hr)	10	-0.60	agree
222	1.9 (48 hr)	10	0.72	agree
224	>1000	>100	[0]	agree
235	4.1 (24 hr)	0.2	-1.30	disagree
237	>1000 (48 hr)	10	-2	disagree
239	NTS >100 (24 hr)	NTS	-	agree
240	37.2 (48 hr)	>100	-0.43	agree
241	24 (48 hr)	>100	0.62	agree

Chem. No.	MPD EC50 value [mg/l]	SAR EC50 value [mg/l]	Difference [± log units]	Result
242	21.1 (48 hr)	>100	0.67	agree
253	NTS	NTS	-	agree
256	>1000 (24 hr)	90	-1.05	disagree
263	250 (24 hr)	17	-1.16	disagree
265	16,940 (48 hr)	>1000	[0]	agree
267	nd	NTS	-	-
268	900 (24 hr)	0.1	-4	disagree
269	NTS >3.7 (48 hr)	NTS	-	agree
270	44 (24 hr)	9	-0.7	agree
271	93 (48 hr)	50	-0.27	agree
275	139.3 (24 hr)	0.42	-2.52	disagree
278	0.53 (48 hr)	11	1.32	disagree
281	0.91 (48 hr)	NTS	-	disagree

Chem. No.	MPD EC50 value [mg/l]	SAR EC50 value [mg/l]	Difference [± log units]	Result
283/ 429	NTS >1000 (24 hr)	NTS	-	agree
286	NTS >100 (48 hr)	NTS	-	agree
287	NTS >1000 (24 hr)	NTS	-	agree
289	NTS >1000 (24 hr)	NTS	-	agree
291	NTS >100 (24 hr)	NTS	-	agree
292	20.5 (24 hr)	3.4	-0.77	agree
300	25 (24 hr)	1.7	-1.16	disagree
307	3.5 (24 hr)	17.4	0.70	agree
309	NTS >0.03 (48 hr)	NTS	-	agree
312	39.7 (24 hr)	1500	1.59	disagree
318	NTS 750 (48 hr)	NTS	-	agree
320	NTS 70 (48 hr)	NTS	-	agree
321	>100 (24 hr)	>100	0	agree

Chem. No.	MPD EC50 value [mg/l]	SAR EC50 value [mg/l]	Difference [± log units]	Result
330	44 (48 hr)	>1000	1.36	disagree
335	>1000 (24 hr)	NTS	-	agree
336	140 (24 hr)	50	-0.44	agree
337	13 (48 hr)	40	0.49	agree
340	25 (48 hr)	≥72	0.46	agree
341	36 (48 hr)	>1000	1.44	disagree
342	>1000 (48 hr)	>1000	0	agree
344	>1000 (24 hr)	>1000	0	agree
348	NTS >1000 (24 hr)	NTS	-	agree
349	6 - 15 (48 hr)	NTS	-	agree
354	>30 (48 hr)	≤14.1	-	-
355	NTS >1 (48 hr)	NTS	-	agree
360	>100 (24 hr)	40	-0.40	agree

Chem. No.	MPD EC50 value [mg/l]	SAR EC50 value [mg/l]	Difference [± log units]	Result
361	NTS >1000 (24 hr)	NTS	-	agree
362	NTS >1.0 (24 hr)	31.3	1.50	disagree
364	1.2 (24 hr)	>100	1.92	disagree
366	1.63 (48 hr)	NTS	-	disagree
368	>5.7 (48 hr)	≥10	0.24	agree
369	602 (48 hr)	400	-0.18	agree
370	125 (24 hr)	0.42	-2.52	disagree
373	20.9 (48 hr)	0.73	-1.52	disagree
376	NTS 172.8 (48 hr)	NTS	-	agree
379	0.78 (48 hr)	0.95	0.08	agree
381	NTS >500 (48 hr)	NTS	-	agree
383	NTS >70 (24 hr)	NTS	-	agree
386	48.9 (48 hr)	≤38.1	-	-

Chem. No.	MPD EC50 value [mg/l]	SAR EC50 value [mg/l]	Difference [± log units]	Result
393	200 (48 hr)	1.6	-2.10	disagree
394	890 (48 hr)	>100	[0]	agree
396	>1000 (24 hr)	>1000	0	agree
398	8.6 (48 hr)	≥10	0.06	agree
401	62 (48 hr)	16	-0.58	agree
406	NTS	NTS	-	agree
411	NTS >1000 (48 hr)	NTS	-	agree
413	NTS >4.8 (24 hr)	NTS	-	agree
414	88 (48 hr)	≥150	0.23	agree
415	NTS >100 (24 hr)	NTS	-	agree
416	NTS >0.0048 (24 hr)	NTS	-	agree
417	NTS	NTS	-	agree
420	1.1 (48 hr)	5.1	0.66	agree

Chem. No.	MPD EC50 value [mg/l]	SAR EC50 value [mg/l]	Difference [± log units]	Result
421	signs for toxicity	0.07	-	-
425	52 (48 hr)	≥30	-0.24	agree
431	NTS >1000 (24 hr)	NTS	-	agree
436	19 (24 hr)	0.06	-2.52	disagree
437	NTS 14 (48 hr)	NTS	-	agree
439	>1000	≥100	[0]	agree
441	70 (48 hr)	10	-0.85	agree
442	176 (24 hr)	≥100	-0.24	agree
443	146 (24 hr)	≥7	-1.30	disagree
444	5.2 (24 hr)	nd	-	-
445	>100	>100	0	agree
446	NTS 62 (24 hr)	NTS	-	agree
451	111 (48 hr)	≤1000	-	-
472	6.36 (48 hr)	NTS	-	disagree

TOXICITY TO ALGAE: COMPARISON OF TEST RESULTS AND PREDICTIONS

Chem. No.	MPD EC50 value [mg/l]	SAR EC50 value [mg/l]	Difference [± log units]	Result
110	NTS	NTS	-	agree
219	9.4	6	-0.19	agree
271	9	10	0.04	agree
366	NTS >12	NTS	-	agree
451	32	≤10	-	-

ACUTE ORAL TOXICITY: COMPARISON OF TEST RESULTS AND PREDICTIONS

Chem. No.	MPD (label)*	SAR	Result
4	(High) (R35)	High	Agree concern
6	Low	Low	Agree
16	Low	Low	Agree
17	Low	Low	Agree
21	Low	Low	Agree
23	Low	Low	Agree
24	Low	Low	Agree
26	Low	Low	Agree
37	Low	Low	Agree
44	Low	Low	Agree
47	Low-Moderate (R22)	Low	SAR low (overlap)
49	Low-Moderate (R22)	Low	SAR low (overlap)
50	Low	Low	Agree

Chem. No.	MPD (label)*	SAR	Result
53	Low	Low	Agree
54	Low-Moderate (R22)	Low	SAT low (overlap)
61	Low	Low	Agree
68	Low	Low	Agree
69	Low	Low	Agree
70	Low	Low	Agree
76	Low	Low	Agree
78	Low	Low	Agree
79	Low	Low	Agree
87	Low	Low	Agree
96	Low	Low	Agree
99	Low	Low	Agree
101	Low	Low	Agree

Chem. No.	MPD (label)*	SAR	Result
102	Low	Low	Agree
106	Low	Low	Agree
107	(High) (R35)	High	Agree concern
108	Low	Low	Agree
110	Low	Low	Agree
113	Low	Low	Agree
118	Low	Low	Agree
124	Low	Moderate	SAR high
128	Low	Low	Agree
133	Low	Low	Agree
144	Low	Low	Agree
148	Low	Low	Agree
151	Low	Low	Agree

Chem. No.	MPD (label)*	SAR	Result
155	Low	Low	Agree
156	Low-Moderate (R22)	Low	SAR lov (overlap)
164	Low	Low	Agree
170	Low	Low	Agree
173	Low	Low	Agree
176	Low	Low	Agree
182	Low	Low	Agree
186	Low	Low	Agree
192	Low	Low	Agree
194	Low	Low	Agree
196	Low	Low	Agree
197	Moderate (R22)	Low	SAR low
200	Low	Low	Agree

Chem. No.	MPD (label)*	SAR	Result
204	Low	Low	Agree
214	Low	Low	Agree
216	Low	Low	Agree
217	Low	Low	Agree
218	Low	Low	Agree
219	Low-Moderate (R22)	Low	SAR low (overlap)
222	Low	Low	Agree
224	Low	Low	Agree
235	Low	Low	Agree
237	Low	Low	Agree
239	Low	Low	Agree
240	Low	Low	Agree
241	Moderate (R22)	Low	SAR low

Chem. No.	MPD (label)*	SAR	Result
242	Moderate (R22)	Low	SAR low
253	Low	Low	Agree
256	Low	Low	Agree
263	Low	Low	Agree
265	Low	Low	Agree
267	Low	Low	Agree
268	Low	Low	Agree
269	Low	Low	Agree
270	Low	Low	Agree
271	Low	Low	Agree
275	Low	Low	Agree
278	Low	Low	Agree
281	Moderate (R22)	Moderate	Agree concern

Chem. No.	MPD (label)*	SAR	Result
283/ 429	Low	Low	Agree
286	Low	Low	Agree
287	Low	Low	Agree
289	Low	Low	Agree
291	Low	Low	Agree
292	Low	Low	Agree
300	Low-Moderate (R22)	Low	SAR low (overlap)
307	Moderate-High (R25)	Low	SAR low
309	Low	Low	Agree
312	Low-Moderate	Low	SAR low (overlap)
318	Low	Low	Agree
320	Low	Low	Agree
321	Low	Low	Agree

Chem. No.	MPD (label)*	SAR	Result
330	Moderate-High (R25)	Low	SAR low
335	Low	Low	Agree
336	Low	Low	Agree
337	Low	Low	Agree
340	Low-Moderate	Low	SAR low (overlap)
341	Low	Low	Agree
342	Low	Low	Agree
344	Low	Low	Agree
348	Low	Low	Agree
349	Low	Low	Agree
354	Low	Low	Agree
355	Low	Low	Agree
360	Low-Moderate (R22)	Low	SAR low (overlap)

Chem. No.	MPD (labal)*	SAR	Result
361	Low	Low	Agree
362	Low	Low	Agree
364	Low	Low	Agree
366	Low	Low	Agree
368	Low	Low	Agree
369	Low	Low	Agree
370	Low-Moderate (R22)	Low	SAR low (overlap)
373	Low	Low	Agree
376	Low	Low	Agree
379	Low	Low	Agree
381	Low	Low	Agree
383	Low	Low	Agree
386	Low	Low	Agree

Chem. No.	MPD (label)*	SAR	Result
393	Low	Low	Agree
394	Low	Low	Agree
396	Low	Low	Agree
398	Low	Low	Agree
401	Low	Low	Agree
406	Low	Low	Agree
411	Low	Low	Agree
413	Low-Moderate (R22)	Low	SAR low (overlap)
414	Low	Low	Agree
415	Low	Low	Agree
416	Low	Low	Agree
417	Low	Low	Agree
420	Low	Low	Agree

Chem. No.	MPD (label)*	SAR	Result
421	Low	Low	Agree
425	Low-Moderate (R22)	Low	SAR low (overlap)
431	Low	Low	Agree
436	Moderate (R22)	Low	SAR low
437	Low	Low	Agree
439	Low	Low	Agree
441	Moderate-High (R22)	Moderate	SAR low (overlap) Agree concern, but not level of concern
442	Low	Low	Agree
443	Moderate-High (R22)	Moderate	SAR low (overlap) Agree concern, but not level of concern
444	Low	Low	Agree
445	Low	Low	Agree
446	Low	Low	Agree
451	Low	Low	Agree
472	Low	Low	Agree

* See Appendix 3 for list of EC labels (R numbers and phrases)

SKIN AND EYE IRRITATION: COMPARISON OF TEST RESULTS AND PREDICTIONS

Chem. No.	Skin MPD (label)[3]	Skin SAR	Skin Result	Eye MPD (label)[3]	Eye SAR	Eye Result
4	(corr.)[1] (R35)	effects predicted	agree	(corr.)[1] (R35)	effects predicted	agree
6	not irritant	no comment	agree	(irritant)[2]	not irritant	SAR low
16	not irritant	no comment	agree	not irritant	no comment	agree
17	not irritant	not irritant	agree	not irritant	not irritant	agree
21	not irritant	no comment	agree	not irritant	no comment	agree
23	slight	slight	agree	slight	slight	agree
24	not irritant	no comment	agree	not irritant	no comment	agree
26	not irritant	no comment	agree	not irritant	no comment	agree
37	not irritant	slight	agree	slight	slight	agree
44	not irritant	not irritant	agree	not irritant	?	agree?
47	not irritant	?	agree?	irritant (R41)	?	SAR low
49	corrosive (R34)	irritant	agree	corrosive (R34)	irritant	agree
50	not irritant	irritant	SAR high	not irritant	irritant	SAR high

Chem. No.	Skin MPD (label)[3]	Skin SAR	Skin Result	Eye MPD (label)[3]	Eye SAR	Eye Result
53	irritant (R38)	irritant	agree	(irritant)[2]	irritant	agree
54	not irritant	no comment	agree	not irritant	no comment	agree
61	not irritant	no comment	agree	not irritant	no comment	agree
68	not irritant	no comment	agree	not irritant	no comment	agree
69	not irritant	not irritant	agree	not irritant	not irritant	agree
70	not irritant	not irritant	agree	not irritant	not irritant	agree
76	not irritant	no comment	agree	not irritant	no comment	agree
78	not irritant	not irritant	agree	not irritant	not irritant	agree
79	not irritant	no comment	agree	not irritant	no comment	agree
87	not irritant	no comment	agree	irritant (R41)	no comment	SAR low
96	not irritant	irritant	SAR high	not irritant	irritant	SAR high
99	not irritant	irritant	SAR high	not irritant	irritant	SAR high
101	not irritant	not irritant	agree	not irritant	irritant	SAR high

Chem. No.	Skin			Eye		
	MPD (label)[3]	SAR	Result	MPD (label)[3]	SAR	Result
102	not irritant	no comment	agree	not irritant	no comment	agree
106	not irritant	no comment	agree	not irritant	no comment	agree
107	(corr.)[1] (R35)	effects predicted	agree	(corr.)[1] (R35)	effects predicted	agree
108	not irritant	no comment	agree	not irritant	no comment	agree
110	not irritant	no comment	agree	not irritant	no comment	agree
113	not irritant	no comment	agree	not irritant	no comment	agree
118	corrosive (R34)	no comment	SAR low	(corr.)[1] (R34)	no comment	SAR low
124	not irritant	irritant	SAR high	irritant (R36)	irritant	agree
128	not irritant	not irritant	agree	not irritant	irritant	SAR high
133	not irritant	no comment	agree	not irritant	no comment	agree
144	not irritant	not irritant	agree	not irritant	not irritant	agree
148	not irritant	no comment	agree	not irritant	no comment	agree
151	not irritant	not irritant	agree	irritant (R36)	irritant	agree

Chem. No.	Skin MPD (label)[3]	Skin SAR	Skin Result	Eye MPD (label)[3]	Eye SAR	Eye Result
155	not irritant	no comment	agree	not irritant	no comment	agree
156	not irritant	?	agree?	not irritant	?	agree?
164	not irritant	irritant	SAR high	not irritant	irritant	SAR high
170	not irritant	irritant	SAR high	irritant (R41)	irritant	agree
173	(irritant)[2]	irritant	agree	(irritant)[2]	irritant	agree
176	not irritant	irritant	SAR high	not irritant	irritant	SAR high
182	corrosive (R34)	not irritant	SAR low	corrosive (R34)	irritant	agree
186	not irritant	no comment	agree	not irritant	no comment	agree
192	corrosive (R34)	no comment	SAR low	corrosive (R34)	no comment	SAR low
194	corrosive (R34)	no comment	SAR low	(corr.)[1] (R34)	no comment	SAR low
196	not irritant	irritant	SAR high	not irritant	irritant	SAR high
197	not irritant	no comment	agree	irritant (R41)	no comment	SAR low
200	not irritant	no comment	agree	not irritant	no comment	agree

Chem. No.	Skin MPD (label)[3]	Skin SAR	Skin Result	Eye MPD (label)[3]	Eye SAR	Eye Result
204	not irritant	no comment	agree	not irritant	no comment	agree
214	not irritant	no comment	agree	not irritant	no comment	agree
216	not irritant	not irritant	agree	not irritant	irritant	SAR high
217	not irritant	no comment	agree	not irritant	no comment	agree
218	not irritant	no comment	agree	not irritant	no comment	agree
219	not irritant	no comment	agree	not irritant	no comment	agree
222	irritant (R38)	irritant	agree	irritant (R36)	irritant	agree
224	slight	slight	agree	slight	slight	agree
235	corrosive (R34)	no comment	SAR low	(corr.)[1] (R34)	no comment	SAR low
237	irritant (R38)	irritant	agree	irritant (R36)	irritant	agree
239	not irritant	no comment	agree	not irritant	no comment	agree
240	(irritant)[2]	irritant	agree	not irritant	irritant	SAR high
241	not irritant	no comment	agree	not irritant	no comment	agree

Chem. No.	Skin MPD (label)[3]	Skin SAR	Skin Result	Eye MPD (label)[3]	Eye SAR	Eye Result
242	not irritant	no comment	agree	not irritant	no comment	agree
253	not irritant	no comment	agree	not irritant	no comment	agree
256	not irritant	irritant	SAR high	irritant (R36)	irritant	agree
263	not irritant	not irritant	agree	irritant (R36)	irritant	Ageree
265	not irritant	no comment	agree	not irritant	no comment	agree
267	ND	no comment	agree	ND	no comment	agree
268	not irritant	not irritant	agree	not irritant	irritant	SAR high
269	not irritant	irritant	SAR high	not irritant	irritant	SAR high
270	not irritant	no comment	agree	irritant (R36)	no comment	SAR low
271	not irritant	irritant	SAR high	not irritant	irritant	SAR high
275	not irritant	no comment	agree	not irritant	no comment	agree
278	irritant (R38)	irritant	agree	(irritant)[2]	irritant	agree
281	not irritant	not irritant	agree	irritant (R36)	irritant	agree

Chem. No.	Skin MPD (label)[3]	Skin SAR	Skin Result	Eye MPD (label)[3]	Eye SAR	Eye Result
283/ 429	not irritant	no comment	agree	not irritant	no comment	agree
286	not irritant	not irritant	agree	not irritant	irritant	SAR high
287	not irritant	no comment	agree	not irritant	no comment	agree
289	not irritant	no comment	agree	not irritant	no comment	agree
291	not irritant	no comment	agree	not irritant	no comment	agree
292	not irritant	mild	agree	not irritant	mild	agree
300	not irritant	no comment	agree	not irritant	no comment	agree
307	not irritant	no comment	agree	not irritant	no comment	agree
309	not irritant	no comment	agree	not irritant	no comment	agree
312	not irritant	no comment	agree	not irritant	no comment	agree
318	not irritant	no comment	agree	not irritant	no comment	agree
320	not irritant	no comment	agree	not irritant	no comment	agree
321	not irritant	no comment	agree	not irritant	no comment	agree

Chem. No.	Skin MPD (label)[3]	Skin SAR	Skin Result	Eye MPD (label)[3]	Eye SAR	Eye Result
330	not irritant	not irritant	agree	(irritant)[2]	irritant	agree
335	not irritant	no comment	agree	not irritant	no comment	agree
336	not irritant	no comment	agree	not irritant	no comment	agree
337	not irritant	no comment	agree	not irritant	no comment	agree
340	not irritant	no comment	agree	(irritant)[2]	no comment	SAR low
341	not irritant	irritant	SAR high	not irritant	irritant	SAR high
342	not irritant	no comment	agree	not irritant	no comment	agree
344	not irritant	no comment	agree	not irritant	no comment	agree
348	not irritant	no comment	agree	not irritant	no comment	agree
349	not irritant	no comment	agree	not irritant	no comment	agree
354	not irritant	no comment	agree	not irritant	no comment	agree
355	not irritant	no comment	agree	not irritant	no comment	agree
360	not irritant	irritant	SAR high	(irritant)[2]	irritant	agree

Chem. No.	Skin MPD (label)[3]	Skin SAR	Skin Result	Eye MPD (label)[3]	Eye SAR	Eye Result
361	not irritant	no comment	agree	not irritant	no comment	agree
362	not irritant	no comment	agree	not irritant	no comment	agree
364	not irritant	no comment	agree	not irritant	no comment	agree
366	not irritant	no comment	agree	not irritant	no comment	agree
368	not irritant	irritant	SAR high	not irritant	irritant	SAR high
369	not irritant	no comment	agree	not irritant	no comment	agree
370	corrosive (R34)	irritant	agree	(corr.)[1] (R34)	irritant	agree
373	irritant (R38)	no comment	SAR low	not irritant	no comment	agree
376	not irritant	irritant	SAR high	not irritant	not irritant	agree
379	not irritant	no comment	agree	not irritant	no comment	agree
381	not irritant	no comment	agree	not irritant	no comment	agree
383	not irritant	no comment	agree	not irritant	no comment	agree
386	not irritant	irritant	SAR high	not irritant	irritant	SAR high

Chem. No.	Skin MPD (label)[3]	Skin SAR	Skin Result	Eye MPD (label)[3]	Eye SAR	Eye Result
393	not irritant	no comment	agree	(irritant)[2]	no comment	SAR low
394	not irritant	no comment	agree	not irritant	no comment	agree
396	not irritant	no comment	agree	not irritant	no comment	agree
398	slight	irritant	agree	slight	irritant	agree
401	not irritant	irritant	SAR high	not irritant	irritant	SAR high
406	not irritant	no comment	agree	not irritant	no comment	agree
411	not irritant	no comment	agree	not irritant	no comment	agree
413	not irritant	no comment	agree	not irritant	no comment	agree
414	not irritant	no comment	agree	not irritant	no comment	agree
415	not irritant	no comment	agree	not irritant	no comment	agree
416	not irritant	no comment	agree	not irritant	no comment	agree
417	not irritant	no comment	agree	not irritant	no comment	agree
420	not irritant	no comment	agree	not irritant	no comment	agree
421	not irritant	no comment	agree	not irritant	no comment	agree

Chem. No.	Skin			Eye		
	MPD (label)[3]	SAR	Result	MPD (label)[3]	SAR	Result
425	corrosive (R34)	irritant	agree	(corr.)[1] (R34)	irritant	agree
431	not irritant	no comment	agree	not irritant	no comment	agree
436	corrosive (R34)	no comment	SAR low	(corr.)[1] (R34)	no comment	SAR low
437	irritant (R38)	irritant	agree	(irritant)[2]	irritant	agree
439	not irritant	no comment	agree	not irritant	no comment	agree
441	not irritant	not irritant	agree	irritant (R41)	irritant	agree
442	not irritant	irritant	SAR high	irritant (R41)	irritant	agree
443	corrosive (R34)	no comment	SAR low	(corr.)[1] (R34)	no comment	SAR low
444	not irritant	no comment	agree	not irritant	no comment	agree
445	not irritant	no comment	agree	not irritant	no comment	agree
446	not irritant	no comment	agree	not irritant	no comment	agree
451	not irritant	no comment	agree	not irritant	no comment	agree
472	not irritant	no comment	agree	not irritant	no comment	agree

[1] substance not tested because assumed corrosive
[2] irritant, below classification level
[3] see Appendix 3 for list of EC labels (R numbers and phrases)
nd: test not done

SYSTEMIC TOXICITY: COMPARISON OF TEST RESULTS AND PREDICTIONS

Chem. No.	SAR level for organ toxicity	MPD level for organ toxicity	SAR concern organ toxicity	MPD target organ toxicity	SAR concern not tested
4	High	High	Acute	nd	
6	Low	Low	nd	nd	
16	Low	Low	None	None	Develop
17	Low	Low	None	None	Develop Repro
21	Low	Low	None	Liver-inc wt NOEL=330mg/kg LOAEL=1000mg/kg	
23	Low	Mod R48	None	Liver-inc wt micros path NOEL=40mg/kg LOAEL=200mg/kg	
24	Low	Mod	None	Liver-micros path NOEL=8mg/kg LOAEL=200mg/kg	
26	Low	Low	None	Liver-clinchem NOEL=200mg/kg LOAEL=1000mg/kg	
37	Low	Low	None	Liver-inc wt clinchem NOEL=750mg/kg LOAEL=1500mg/kg	Develop Devel-neuro Neuro

Chem. No.	SAR level for organ toxicity	MPD level for organ toxicity	SAR concern organ toxicity	MPD target organ toxicity	SAR concern not tested
44	Low	Low	Liver (uncert)	None	
47	Low	Mod R48	None	Liver-inc wt clinchem kidney-inc BUN NOEL(m)=50mg/kg NOEL(f)=5mg/kg LOAEL(m)=500mg/kg LOAEL(f)=50mg/kg	
49	Low	Low-mod	None	Skin Adrenal NOEL<100mg/kg	Develop
50	Low	Low	None	None	
53	Low	Low	None	Liver-clinchem @ <200mg/kg(f) NOEL=200mg/kg(m)	Immuno Develop
54	Mod	Mod-high	Neuro Hemo-siderosis Eye (cataracts)	Neuro Liver Eye NOEL<100mg/kg Death at 300mg/kg	
61	Low	Low-mod	None	Blood effects Kidney-urinalysis Lymph nodes-hyperplasia NOEL=200mg/kg LOAEL=1000mg/kg	

Chem. No.	SAR level for organ toxicity	MPD level for organ toxicity	SAR concern organ toxicity	MPD target organ toxicity	SAR concern not tested
68	Low	Low	None	Liver-mircos path Kidney-inc wt micros path NOEL < 1gm/kg	Onco
69	Low	Low	None	None	Onco
70	Low	Low	None	Liver-clinchem NOEL=1000ppm (70-100mg/kg) LOAEL=5000ppm	
76	Mod-high	Mod-high	Liver Kidney Thymus Spleen Repro	Liver-inc wt micros path Kidney-inc wt micros path Bone Marrrow NOEL=10mg/kg/28-days LOAEL=50mg/kg/28-days NOEL=5mg/kg/90-days	Develop
78	Low	Low	None	None	Onco
79	Low	Low	None	None	
87	Low	Low	None	Liver-clin chem Kidney-micros path NOEL=120mg/kg LOAEL=1200mg/kg	
96	Low-mod	Low	Blood (hemolytic anemia)	Testes-dec wt Neuro-locomotor activity disturbance NOEL=250mg/kg LOAEL=1g/kg	Onco Devel

Chem. No.	SAR level for organ toxicity	MPD level for organ toxicity	SAR concern organ toxicity	MPD target organ toxicity	SAR concern not tested
99	Low-mod	Low	Liver	None	
101	Low	Low	None	None	Onco Resp sens
102	Low-mod	Low	Liver (uncert)	None	Develop Onco
106	Low	Low	None	None	
107	Mod-high	Mod-high	Acute	nd	
108	Mod	Mod	Liver Kidney	Liver-micros path, clinchem Kidney-clinchem Neutrophils,monocytes NOEL=30mg/kg LOAEL=100mg/kg	Develop
110	Low	Low	None	Liver-inc enzymes, dec bw NOEL=1ml/kg LOAEL=2ml/kg	
113	Low	Low	None	None	
118	Low	Low-mod	None	Stomach NOEL=60mg/kg LOAEL=200mg/kg	Develop Neuro

Chem. No.	SAR level for organ toxicity	MPD level for organ toxicity	SAR concern organ toxicity	MPD target organ toxicity	SAR concern not tested
156	Low	Mod-high R48	Cholin-esterace inhibition	Liver-micros path Kidney-micros path NOEL=1-2mg/kg-90-day study LOAEL=50mg/kg-90-day study NOEL=15mg/kg-28-day study	Develop Neuro
164	Low	Low	None	None	
170	Low-mod	Low-mod	Blood	Liver-micros path kidney-micros path NOEL=40-360mg/kg LOAEL=360mg/kg	Develop Devel-neuro
173	Low	Low-mod	None	Poor health NOEL=300mg/kg LOEL=1000mg/kg-death	
176	Low	Low-mod	None	Kidney-clinchem Liver-clinchem NOEL=33-35mg/kg LOAEL=280mg/kg	
182	Low	Low	None	Clin chem NOEL=50mg/kg LOAEL(f)=150mg/kg Cor-s, Irr-e	
186	High	Mod	Liver	Seminal vesicles-micro path,atrophy Uterus-micro path,atrophy Ovaries-micro path,atrophy NOEL=33mg/kg LOAEL=130mg/kg	Onco

Chem. No.	SAR level for organ toxicity	MPD level for organ toxicity	SAR concern organ toxicity	MPD target organ toxicity	SAR concern not tested
124	Mod-high	Mod	Chronic Acute	Liver-dec wt Blood NOEL=10mg/kg LOAEL=30mg/kg	Develop Repro
128	Low	Low	None	None	
133	Low	Low-mod	None	Degeneration of gastric lining, regression of thymus, bone marrow NOEL=20mg/kg LOAEL=100mg/kg	
144	Low	Low	None	Dec bw NOEL=100mg/kg LOAEL=1000mg/kg	
148	Low	Low	None	None	
151	Low-mod	Mod-high	Lung	Liver-micros path Testes-micros path Ovary-micros path Kidney-clinchem Neuro-dose-dep agitation,uncor movement NOEL<10mg/kg	
155	Low-mod	Low	Liver Kidney	None	Develop Repro

Chem. No.	SAR level for organ toxicity	MPD level for organ toxicity	SAR concern organ toxicity	MPD target organ toxicity	SAR concern not tested
192	Low	Low-mod	None	Kidney-micros path NOEL=40mg/kg LOAEL=400mg/kg	Develop
194	Low	Low	None	nd	
196	Low-mod	Low-mod	Liver	Blood-inc prothrombin time dec platelets,dec WBC NOEL=200mg/kg LOAEL=1000mg/kg	Onco Develop
197	Low	Mod-high R48	None	Kidney-inc wt, micros path Blood-anemia, cyanosis, sulphmethemoglobin Liver-inc wt, clinchem NOEL<10mg/kg Sens	Onco
200	Mod	Mod-high R48	Repro,liverkidney	Testes-dec wt, micros path Liver-micros path Kidney-mircos path, clinchem Spleen-lym depletion NOEL<10mg/kg	Neuro Repro
204	Low	Low	Chelator	Clinchem NOEL=170-350mg/kg LOAEL=850-1750mg/kg	Develop

Chem. No.	SAR level for organ toxicity	MPD level for organ toxicity	SAR concern organ toxicity	MPD target organ toxicity	SAR concern not tested
214	Low	Low	None	Clinchem NOEL=200mg/kg LOAEL=600mg/kg	
216	Low	Low-mod	None	Blood-inc RBCs and WBCs NOEL=50mg/kg LOAEL=200mg/kg	Neuro Photosens
217	Low	Low	None	None	
218	Low	Low-mod	None	Liver-inc wt Kidney-inc wt NOEL=2.2mg/kg (30ppm) LOAEL=23-26mg/kg (100ppm)	Develop Repro
219	Mod	Low	Blood Liver	Undefined NOEL>300mg/kg	Onco Develop Repro
222	Low	High R48	None	Derm sens Undefined eff @ 0.3-0.9mg/m^3	Onco Resp sens Repro
224	Low	Low	None	None	Onco
235	Low-mod	Mod	Liver, Thyroid	Liver-micros path, clin chem, inc wt Adrenals-micros path, inc wt Lung-micro path Blood-malform RBCs,inc WBCs NOEL=50mg/kg LOAEL=150mg/kg	Develop Onco

Chem. No.	SAR level for organ toxicity	MPD level for organ toxicity	SAR concern organ toxicity	MPD target organ toxicity	SAR concern not tested
237	Low-mod	Low-mod	Liver Lung	Kidney-micros path, urinalysis NOEL=100mg/kg LOAEL=300mg/kg	Lung
239	Low	Low	None	None	
240	Low	Low-mod	None	Liver-inc wt Kidney-inc wt NOEL=40mg/kg LOAEL=200mg/kg Lysomal storage of dye @1000mg/kg	Onco
241	Low	Low	None	Acute LD_{50} = 585mg/kg Inc serum Cl NOEL=30mg/kg LOAEL=100mg/kg	Neuro
242	Low	Low-mod	None	Acute LD_{50} = 520mg/kg Kidney-micros path,inc wt Liver- inc wt Adrenals-inc wt Blood-inc WBC and Hb NOEL=50mg/kg LOAEL=150mg/kg	Neuro
253	Low	Low-mod	None	Liver-inc wt, clinchem NOEL=50mg/kg LOAEL=250mg/kg	Develop

Chem. No.	SAR level for organ toxicity	MPD level for organ toxicity	SAR concern organ toxicity	MPD target organ toxicity	SAR concern not tested
256	Low	Low-mod	None	Blood-inc WBC and platelets Liver-inc wt Kidney-inc wt and clinchem NOEL=50mg/kg LOAEL=200mg/kg	
263	Mod	Low	Kidney	Dec bw clinchem NOEL=200mg/kg LOAEL=1000mg/kg	Onco Develop Repro Neuro
265	Low	Low-mod	None	Liver-inc wt, clinchem NOEL=30mg/kg LOAEL=100mg/kg	
267	Low	Low	None	nd	
268	Low-mod	Low	Liver Kidney Blood	Kidney-micros path, clinchem, urinalysis Liver-micros path,clinchem NOEL=250mg/kg LOAEL=1000mg/kg	Neuro
269	Low	Low-mod	None	Liver-micros path, clinchem, inc wt NOEL<100mg/kg	
270	Mod	Low-mod	Liver Spleen Thymus	Liver-micros path Spleen-micros path Heart-micros path NOEL=46-52mg/kg LOAEL=120-133mg/kg	Neuro Develop

Chem. No.	SAR level for organ toxicity	MPD level for organ toxicity	SAR concern organ toxicity	MPD target organ toxicity	SAR concern not tested
271	Low	Low-mod	None	Liver-micros path, clinchem Kidney-inc wt NOEL=40mg/kg LOAEL=200mg/kg	
275	Mod	Low	Blood Liver	None	Onco Develop

278	Low	Low-mod	None	Liver-micros path, inc wt Kidney-inc wt
				Blood-dec #RBCs
				NOEL=100mg/kg
				LOAEL=500mg/kg	

281	Low	Mod R48	None	Liver-micros path, inc wt, clinchem Kidney-inc wt, clinchem Blood-dec platelets,WBC Acute-oral LD_{50}=850mg/kg NOEL=5-10mg/kg LOAEL=15mg/kg	
283/429	Low	Low	None	None	
286	Low	Low	None	None	
287	Low	Low	None	None	
289	Low-mod	Low	Liver Blood	Liver-inc wt (m) Kidney-inc wt (m) NOEL=200mg/kg LOAEL=1000mg/kg	Develop Onco
291	Low	Low	None	None	

Chem. No.	SAR level for organ toxicity	MPD level for organ toxicity	SAR concern organ toxicity	MPD target organ toxicity	SAR concern not tested
292	Mod-high	Mod-high	Multiple	Adrenals,liver, blood, NOEL<50mg/kg	Product lit
300	Low	Mod	None	Liver-micros path, clinchem Blood-dec#RBC, clot factor, inc proth time, PTT Neuro-clin signs NOEL=20mg/kg LOAEL=100mg/kg	
307	Mod	Mod	Blood Liver	Blood-dec platelets, WBC, lym; inc RBC, neutro NOEL=11mg/kg LOAEL=45mg/kg Acute LD_{50} = 88mg/kg	Develop Repro Onco
309	Low-mod	Low	Liver	NOEL=41,500ppm	Onco
312	Low-mod	Low-mod	Blood	Liver-micros path, inc wt Kidney-inc wt Blood-hemolysis, dec RBC, hemosiderosis, extramedullary hemotopoesis NOEL=100mg/kg LOAEL=300mg/kg	Develop Onco
318	Low	Low	None	None	Develop Neuro Onco

Chem. No.	SAR level for organ toxicity	MPD level for organ toxicity	SAR concern organ toxicity	MPD target organ toxicity	SAR concern not tested
320	Low	Low	None	Clinchem NOEL=250mg/kg LOAEL= 1000mg/kg	None
321	Low	Low-mod	None	Undefined NOEL = 50mg/kg	Develop
330	Mod	Mod	Kidney Liver	Kidney-Clinchem Dec lymphocytes NOEL=1mg/kg LOAEL=10mg/kg Acute-LD_{50} = 104mg/kg	Develop Neuro Onco
335	Low	Low-mod		Liver-clin chem Blood-inc#WBC & reticulocytes NOEL=50mg/kg LOAEL=200mg/kg	Onco Develop Neuro
336	Low	Low	None	Dec organ ratio wts-liver/body, liver/brain NOEL=250mg/kg LOAEL=1000mg/kg	Develop
337	nd	Low-mod	nd	NOEL=160mg/kg/90-days Liver-inc wt Thyroid-micros Kidney-hyaline droplets	

Chem. No.	SAR level for organ toxicity	MPD level for organ toxicity	SAR concern organ toxicity	MPD target organ toxicity	SAR concern not tested
340	Mod	Low	Bone marrow CNS effects	Liver-clinchem,inc wt NOEL=80mg/kg LOAEL=400mg/kg	Develop Neuro
341	Low	Low	None	None	Develop Onco
342	Low	Low	None	Kidney-clinchem Blood-WBC-dec lymphocytes Neuro-clin sign NOEL=500mg/kg LOAEL=1000mg/kg	
344	Low	Low		None	Develop Onco
348	Low	Low	None	None	
349	Low	Mod	None	Liver-micros path, clinchem Kidney-micros path, clinchem Spleen-micros path, clinchem Blood-dec#RBC, hemosiderin NOEL=10mg/kg LOAEL=100mg/kg	

354	Low	Low	None	Liver-micros path, inc wt
				Blood-dec #RBC
				NOEL=78-90mg/kg(1000ppm)
				LOAEL=234-272mg/kg (3000ppm)
					Develop
					Neuro

355	Low	Low	None	None	

Chem. No.	SAR level for organ toxicity	MPD level for organ toxicity	SAR concern organ toxicity	MPD target organ toxicity	SAR concern not tested
360	Low-mod	Low-mod	Blood	Liver-micros path,clinchem Blood-inc#RBC, micros NOEL=50mg/kg LOAEL=300mg/kg	Develop Neuro
361	Low	Low	None	None	
362	Mod	Low-mod	Blood Liver	Undefined effects NOEL=50mg/kg LOAEL=150mg/kg	Develop Onco
364	Low-mod	Low	Liver Blood	Kidney-micros path,clinchem,urinalysis Liver-clin chem NOEL=200mg/kg LOAEL=1000mg/kg	Develop Neuro
366	Low	Low	None	None	
368	Low-mod	Low-mod	Kidney Liver	Liver-inc wt Kidney-micros path, inc wt, urinalysis NOEL=40mg/kg LOAEL=200mg/kg	
369	Low	Low	None	Undefined NOEL= 200mg/kg LOAEL=1000mg/kg	
370	Mod	Mod	Liver Kidney	Liver-clin chem Stomach-micros path NOEL=50mg/kg LOAEL=170mg/kg 1/12 died at 170mg/kg	Develop Onco Neuro

Chem. No.	SAR level for organ toxicity	MPD level for organ toxicity	SAR concern organ toxicity	MPD target organ toxicity	SAR concern not tested
373	Low-mod	Low-mod	Liver Kidney	Liver-inc wt, clin chem NOEL=50mg/kg LOAEL=250mg/kg	Develop Neuro
376	Low	Low	None	None	
379	Low	Low-mod	None	Kidney-micros path,clinchem, inc wt Liver-inc wt clin chem Blood-micros RBC NOEL=80mg/kg LOAEL=250mg/kg	Repro Onco Neuro
381	Low	Low	None	None	
383	Low	Low	None	None	
386	Low-mod	Low-mod	Liver Kidney	Kidney-inc BUN NOEL=10mg/kg-90 day study LOAEL=50mg/kg-90 day study	
393	Low	Low	None	Adrenal rel wt inc LOAEL=1000mg/kg	
394	Low-mod	Low-mod	Blood	Liver-clin chem NOEL=83mg/kg LOAEL=333mg/kg	Develop
396	Low	Low	None	None	
398	Low-mod	Low	Kidney Liver Lung	Liver-inc wt NOEL=250mg/kg LOAEL=1000mg/kg	

Chem. No.	SAR level for organ toxicity	MPD level for organ toxicity	SAR concern organ toxicity	MPD target organ toxicity	SAR concern not tested
401	Low-mod	Low-mod	CNS	Blood-clot fact, increase in prothom time, dec globulin NOEL=40mg/kg LOAEL=200mg/kg	
406	Mod	Low	Liver	None NOEL>20,000ppm	Repro Onco
411	Low	Low	None	None	
413	Low	Low-mod	None	Liver-micros path Stomach-micros path Testes-micros path Thymus-micros path NOEL=50mg/kg LOAEL-200mg/kg	
414	Mod	Mod R48	Cataracts	Liver-micros path Thyroid-inc wt (dose related) NOEL<2mg/kg-90-day study LOAEL=20mg/kg-90-day study	Develop
415	Low	Low	None	None	
416	Low	Low	None	None	
417	Low	Low	None	None	
420	Low	Mod	None	Liver-micros path,clinchem, inc wt Kidney-micros path, clinchem, inc wt NOEL=15mg/kg LOAEL=60mg/kg	

Chem. No.	SAR level for organ toxicity	MPD level for organ toxicity	SAR concern organ toxicity	MPD target organ toxicity	SAR concern not tested
421	Low	Low-mod	None	Liver-micros path, clinchem, inc wt Kidney-micros path, clinchem, inc wt NOEL≤50mg/kg LOAEL=200mg/kg	
425	Low	Low	None Develop Neuro Testes	Liver inc wt(f) NOEL=100mg/kg LOAEL=500mg/kg	Develop Neuro Repro
431	Low	Low-mod	None	Neuro-clin signs Bone marrow-dec platelets,serum Hb NOEL=30mg/kg LOAEL=200mg/kg	
436	Low	Mod	None	Lung-clin signs Kidney-micros path NOEL=15mg/kg LOAEL=50mg/kg	
437	Low-mod	Low-mod	Blood	Skin-micros path, clin signs NOEL<25mg/kg	
439	Low	Low	None	None	
441	Low	Mod	None	Liver-inc wt, clinchem Bone marrow-hematology NOEL=12mg/kg LOAEL=60mg/kg	Develop Onco

Chem. No.	SAR level for organ toxicity	MPD level for organ toxicity	SAR concern organ toxicity	MPD target organ toxicity	SAR concern not tested
442	Low-mod	Low	Liver	Liver-clinchem NOEL=75mg/kg LOAEL=750mg/kg	Develop Onco
443	Low	Low	None	Liver-clin chem Kidney-clin chem Testes-hemorrhage Brain-hemorrhage Lung-micros path Nose-micros path GI-micro path Acute-LC_{50}=7.6mg/L NOEL < 1.5mg/L Corrosive	
444	Low	Mod	None	Liver-inc wt, clinchem Kidney-micros path, inc wt Neuro-clin sign Skin-gross path NOEL=50mg/kg LOAEL=225mg/kg	Repro Onco
445	Low	Low	None	nd	
446	Low	Mod	None	Liver-micros path,clinchem Kidney-micros path NOEL=0.6-0.7mg/kg(8ppm) LOAEL 3.2-3.3mg/kg	Onco

Chem. No.	SAR level for organ toxicity	MPD level for organ toxicity	SAR concern organ toxicity	MPD target organ toxicity	SAR concern not tested
451	Low	Low	CNS Depression	Liver-inc wt, clinchem Stomach-micros path NOEL=50mg/kg LOAEL=500mg/kg	
472	Low	Low	None	None	

micros path = microscopic pathology

MUTAGENICITY: COMPARISON OF TEST RESULTS AND PREDICTIONS

Chem. No.	MPD result in vitro	MPD result in vivo	SAR	Agreement?
4	nd	nd	0	?
6	Sal -ve	mnuc -ve	0	Yes
16	Sal -ve MCGM +ve	nd	0	No SAR low
17	Sal +ve MCGM -ve	nd	0	No SAR low
21	Sal -ve	mnuc -ve	0	Yes
23	Sal -ve	mnuc -ve	0	Yes
24	Sal -ve	mnuc -ve	0	Yes
26	Sal -ve	mnuc -ve	0	Yes
37	Sal -ve	mnuc -ve	L-M	No EC low
44	Sal -ve	mnuc -ve	0	Yes
47	Sal -ve	mnuc -ve	0	Yes
49	Sal -ve MCGM -ve	nd	0	Yes
50	Sal -ve IVC -ve	nd	0	Yes

Chem. No.	MPD result in vitro	MPD result in vivo	SAR	Agreement?
53	Sal -ve	mnuc -ve	0	Yes
54	Sal weak +ve MCGM -ve	SCE -ve NA -ve	equivocal	Yes
61	Sal -ve IVC -ve	nd	0	Yes
68	Sal -ve IVC -ve	nd	0	Yes
69	Sal -ve E Coli -ve	mnuc -ve	0	Yes
70	Sal -ve	mnuc -ve	0	Yes
76	Sal -ve UDS -ve	mnuc -ve	0	Yes
78	Sal -ve	mnuc -ve	0	Yes
79	Sal -ve E Coli -ve	mnuc -ve	0	Yes
87	Sal -ve IVC -ve	nd	0	Yes
96	Sal -ve E Coli -ve	mnuc -ve	L-M	No EC low
99	Sal -ve IVC -ve	mnuc -ve	0	Yes
101	Sal -ve	mnuc -ve	L-M	No EC low

Chem. No.	MPD result in vitro	MPD result in vivo	SAR	Agreement?
102	Sal -ve	mnuc -ve	L-M	No EC low
106	Sal -ve E Coli -ve	mnuc -ve	0	Yes
107	nd	nd	0	?
108	Sal -ve	mnuc -ve	0	Yes
110	Sal -ve MCGM -ve IVC -ve	mnuc -ve	0	Yes
113	Sal -ve	mnuc-ve	0	Yes
118	Sal -ve	NA -ve mnuc -ve	0	Yes
124	Sal -ve	mnuc -ve	0	Yes
128	Sal -ve	CA -ve	0	Yes
133	Sal -ve	mnuc -ve	0	Yes
144	Sal -ve MCGM -ve IVC -ve	nd	0	Yes
148	Sal -ve	mnuc -ve	0	Yes
151	Sal -ve MCGM -ve IVC -ve	nd	0	Yes

Chem. No.	MPD result in vitro	MPD result in vivo	SAR	Agreement?
155	Sal -ve	mnuc -ve	0	Yes
156	Sal -ve	mnuc -ve	0	Yes
164	Sal -ve SCE -ve	mnuc -ve	0	Yes
170	Sal +ve	mnuc -ve	0	No SAR low
173	Sal -ve	mnuc-ve	0	Yes
176	Sal -ve	mnuc -ve	0	Yes
182	Sal -ve MCGM -ve	mnuc -ve	0	Yes
186	Sal -ve	mnuc -ve	0	Yes
192	Sal -ve E Coli -ve	mnuc -ve	0	Yes
194	nd	nd	0	Yes
196	Sal -ve IVC weak +ve	mnuc -ve	L-M	Yes
197	Sal weak +ve E Coli -ve IVC -ve	nd	L-M	Yes
200	Sal -ve IVC -ve	nd	0	Yes

Chem. No.	MPD result in vitro	MPD result in vivo	SAR	Agreement?
204	Sal -ve	mnuc -ve	0	Yes
214	Sal -ve	mnuc -ve	0	Yes
216	Sal weak +ve MCGM -ve IVC -ve	NA -ve mnuc -ve	0	No SAR low
217	Sal -ve	mnuc -ve	0	Yes
218	Sal -ve E Coli -ve IVC -ve	nd	0	Yes
219	Sal +ve MCGM -ve	mnuc -ve	L-M	Yes
222	Sal -ve	mnuc -ve	L-M	No EC low
224	Sal -ve	mnuc -ve	L-M	No EC low
235	Sal -ve	mnuc -ve	0	Yes
237	Sal -ve IVC -ve	nd	0	Yes
239	Sal -ve IVC -ve	nd	0	Yes
240	Sal -ve	mnuc -ve	0	Yes
241	Sal -ve IVC -ve	nd	0	Yes

Chem. No.	MPD result in vitro	MPD result in vivo	SAR	Agreement?
242	Sal -ve IVC -ve	nd	0	Yes
253	Sal -ve	mnuc -ve	0	Yes
256	Sal -ve	mnuc -ve	0	Yes
263	Sal +ve IVC -ve	mnuc -ve	L-M	Yes
265	Sal -ve IVC -ve	nd	0	Yes
267	nd	nd	0	Yes
268	Sal -ve	mnuc -ve	0	Yes
269	Sal weak +ve MCGM -ve IVC -ve	mnuc -ve	L-M	Yes
270	Sal -ve	mnuc -ve	0	Yes
271	Sal -ve IVC -ve	nd	0	Yes
275	Sal +ve IVC -ve	mnuc -ve	L-M	Yes
278	Sal -ve SCE weak +ve ?	mnuc -ve	0	Yes
281	Sal -ve	mnuc -ve	L	Yes

Chem. No.	MPD result in vitro	MPD result in vivo	SAR	Agreement?
283/ 429	Sal -ve	mnuc-ve	0	Yes
286	Sal -ve	mnuc -ve	0	Yes
287	Sal -ve	mnuc -ve	0	Yes
289	Sal +ve IVC -ve	mnuc -ve	L-M	Yes
291	Sal -ve	mnuc -ve	L	Yes
292	Sal -ve IVC -ve	nd	0	Yes
300	Sal -ve	mnuc -ve	0	Yes
307	Sal +ve E Coli -ve	mnuc -ve	L-M	Yes
309	Sal -ve	mnuc -ve	0	Yes
312	Sal +ve MCGM -ve	mnuc - ve	L -M	Yes
318	Sal -ve	mnuc -ve	0	Yes
320	Sal -ve	mnuc -ve	0	Yes
321	Sal -ve	mnuc -ve	M	No EC low

Chem. No.	MPD result in vitro	MPD result in vivo	SAR	Agreement?
330	Sal -ve	mnuc -ve	L-M	No
335	Sal +ve MCGM -ve	mnuc -ve	L-M	Yes
336	Sal -ve	mnuc -ve	0	Yes
337	Sal -ve MCGM -ve IVC -ve	nd	L-M	No EC low
340	Sal -ve IVC +ve	mnuc -ve	0	No SAR low
341	Sal -ve	mnuc -ve	0	Yes
342	Sal -ve IVC -ve	mnuc -ve	0	Yes
344	Sal -ve	mnuc -ve	0	Yes
348	Sal -ve	mnuc -ve	0	Yes
349	Sal -ve	mnuc -ve	0	Yes
354	Sal -ve IVC -ve SCE -ve	mnuc -ve	0	Yes
355	Sal -ve	mnuc -ve	0	Yes
360	Sal -ve IVC -ve	nd	0	Yes

Chem. No.	MPD result in vitro	MPD result in vivo	SAR	Agreement?
361	Sal -ve. IVC -ve	nd	0	Yes
362	Sal weak +ve	mnuc -ve	L-M	Yes
364	Sal -ve IVC +ve	mnuc -ve	0	No SAR low
366	Sal -ve E Coli -ve	mnuc -ve	0	Yes
368	Sal -ve IVC -ve	nd	0	Yes
369	Sal -ve IVC +ve (art)	mnuc -ve	0	Yes
370	Sal -ve	mnuc -ve	0	Yes
373	Sal -ve	mnuc -ve	0	Yes
376	Sal -ve. IVC -ve	nd	0	Yes
379	Sal -ve IVC -ve	nd	L-M	No EC low
381	Sal -ve	mnuc -ve	0	Yes
383	Sal -ve	mnuc -ve	0	Yes
386	Sal -ve E Coli -ve IVC -ve	mnuc -ve	0	Yes

Chem. No.	MPD result in vitro	MPD result in vivo	SAR	Agreement?
393	Sal -ve	CA -ve	0	Yes
394	Sal -ve IVC -ve	nd	0	Yes
396	Sal -ve	mnuc -ve	0	Yes
398	Sal -ve	mnuc -ve	0	Yes
401	Sal -ve IVC v.weak +ve	nd	0	Yes
406	Sal -ve IVC -ve	nd	L-M	No EC low
411	Sal -ve Prival -ve	mnuc -ve	0	Yes
413	Sal -ve	mnuc -ve	0	Yes
414	Sal -ve	mnuc -ve	0	Yes
415	Sal -ve	mnuc -ve	0	Yes
416	Sal -ve	mnuc -ve	0	Yes
417	Sal -ve	mnuc -ve	0	Yes
420	Sal -ve E Coli -ve IVC -ve	nd	0	Yes

Chem. No.	MPD result in vitro	MPD result in vivo	SAR	Agreement?
421	Sal -ve	mnuc -ve	0	Yes
425	Sal -ve IVC -ve	nd	0	Yes
431	Sal -ve IVC -ve	nd	0	Yes
436	Sal -ve	CA -ve	0	Yes
437	Sal -ve IVC -ve	mnuc -ve	0	Yes
439	Sal -ve IVC -ve	nd	0	Yes
441	Sal -ve E Coli -ve IVC -ve	nd	L-M	No EC low
442	Sal -ve IVC +ve	nd	L-M	Yes
443	Sal -ve	mnuc -ve	0	Yes
444	Sal -ve	mnuc -ve	L-M	No EC low
445	nd	nd	0	Yes
446	Sal -ve E Coli -ve	mnuc -ve	0	Yes
451	Sal -ve E Coli -ve IVC -ve	mnuc -ve	0	Yes
472	Sal -ve	mnuc -ve	0	Yes

Abbreviations:

Sal = Salmonella (Ames) gene mutation test
mnuc = micronucleus test
MCGM = any mammalian cell gene mutation test
IVC = in vitro chromosome aberration test
SCE = sister chromatid exchange test
UDS = unscheduled DNA synthesis test
NA = nuclear anomaly test
CA = chromosome aberration test
E coli = E coli gene mutation test
art = artefact
nd = not done
0 or L = SAR prediction of low concern
L-M = SAR prediction of low to moderata concern
M = SAR prediction of moderate concern
+ve = positive
-ve = negative

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COUNCIL DIRECTIVE

of 18 September 1979

amending for the sixth time Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances

(79/831/EEC)

THE COUNCIL OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Economic Community, and in particular Article 100 thereof,

Having regard to the proposal from the Commission,

Having regard to the opinion of the European Parliament (1),

Having regard to the opinion of the Economic and Social Committee (2),

Whereas to protect man and the environment against potential risks which could arise from the placing on the market of new substances, it is necessary to lay down appropriate measures and in particular to reinforce the recommendations provided in Council Directive 67/548/EEC of 27 June 1967 on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances (3), as last amended by Directive 75/409/EEC (4);

Whereas it is necessary for these reasons to amend Directive 67/548/EEC which at the moment by an adequate classification, packaging and labelling of dangerous substances protects the population and principally the workers using them;

Whereas in order to control the effects on man and the environment it is advisable that any new substance placed on the market be subjected to a prior study by the manufacturer or importer and a notification to the competent authorities conveying mandatorily certain information; whereas it is, moreover, important to follow closely the evolution and use of new substances placed on the market, and that in order to do this it is necessary to institute a system which allows all new substances to be listed;

Whereas, moreover, it is necessary, if the Directive is to be properly applied, to draw up an inventory of substances on the Community market by 18 September 1981;

Whereas it is necessary to provide for measures making it possible to introduce a procedure of notification to one Member State which is then valid for the Community; whereas, it is, moreover, necessary to provide that the measures relating to the classification and labelling of substances may be laid down at Community level;

Whereas it is necessary to introduce measures for the packaging and provisional labelling of dangerous substances not yet appearing in Annex I to Directive 67/548/EEC;

Whereas it is necessary to make the indication of safety advice obligatory;

Whereas Article 2 of the abovementioned Directive classifies substances and preparations as toxic, harmful, corrosive or irritant by the use of general definitions; whereas experience has shown that it is necessary to improve this classification; whereas in the absence, at the moment, of specifications necessary for allocation to these classes, it seems appropriate to provide precise criteria for classification; whereas in addition Article 3 of the Directive provides for an evaluation of danger for the environment and it is therefore necessary to enumerate certain characteristics and parameters of assessment, and to establish a phased study programme,

HAS ADOPTED THIS DIRECTIVE:

Article 1

Articles 1 to 8 of Directive 67/548/EEC are hereby replaced by the following Articles:

'*Article 1*

1. The purpose of this Directive is to approximate the laws, regulations and administrative provisions of the Member States on:

(1) OJ No C 30, 7. 2. 1977, p. 35.
(2) OJ No C 114, 11. 5. 1977, p. 20.
(3) OJ No 196, 16. 8. 1967, p. 1.
(4) OJ No L 183, 14. 7. 1975, p. 22.

(a) the notification of substances, and

(b) the classification, packaging and labelling of substances dangerous to man and the environment,

which are placed on the market in the Member States.

2. This Directive does not apply to the provisions relating to:

(a) medicinal products, narcotics and radioactive substances;

(b) the carriage of dangerous substances by rail, road, inland waterway, sea or air;

(c) foodstuffs or feedingstuffs;

(d) substances in the form of waste which are covered by Council Directive 75/442/EEC of 15 July 1975 relating to waste [1] and Council Directive 78/319/EEC of 20 March 1978 relating to toxic and dangerous waste [2];

(e) substances in transit which are under customs supervision provided they do not undergo any treatment or processing.

3. Articles 15, 16 and 17 do not apply to the provisions governing:

(a) containers which contain gases compressed, liquefied or dissolved under pressure, excluding aerosols which comply with the requirements of Council Directive 75/324/EEC of 20 May 1975 on the approximation of the laws of the Member States relating to aerosol dispensers [3];

(b) munitions and explosives placed on the market with a view to producing a practical effect by explosion or a pyrotechnic effect.

4. Articles 5, 6 and 7, in so far as they are concerned with notification, do not apply:

(a) — until six months after publication of the inventory referred to in Article 13 (1), to substances placed on the market before 18 September 1981;

— six months after publication of the inventory referred to in Article 13 (1), to substances which appear in that inventory;

(b) to pesticides and fertilizers, in as far as they are subject to approval procedures which are at least equivalent or Community notification procedures or procedures which are not yet harmonized;

(c) to substances which are already subject to similar testing and notification requirements under existing Directives.

Article 2

1. For the purpose of this Directive:

(a) "substances" means chemical elements and their compounds as they occur in the natural state or as produced by industry, including any additives required for the purpose of placing them on the market;

(b) "preparations" means mixtures or solutions composed of two or more substances;

(c) "environment" means water, air and land and their inter-relationship as well as relationships between them and any living organisms;

(d) "notification" means the documents whereby the manufacturer or any other person established in the Community who places a substance on its own or in a preparation on the market presents the requisite information to the competent authority of a Member State. The person so doing shall hereinafter be referred to as "the notifier";

(e) "placing on the market" means supplying or making available to third parties.

Importation into Community customs territory shall be deemed to be placing on the market for the purposes of this Directive.

2. The following substances and preparations are "dangerous" within the meaning of this Directive:

(a) explosive:

substances and preparations which may explode under the effect of flame or which are more sensitive to shocks or friction than dinitrobenzene;

(b) oxidizing:

substances and preparations which give rise to highly exothermic reaction when in contact with other substances, particularly flammable substances;

(c) extremely flammable:

liquid substances and preparations having a flash point lower than 0 °C and a boiling point lower than or equal to 35 °C;

(1) OJ No L 194, 15. 7. 1975, p. 39.
(2) OJ No L 84, 31. 3. 1978, p. 43.
(3) OJ No L 147, 9. 6. 1975, p. 40.

(d) highly flammable:
- substances and preparations which may become hot and finally catch fire in contact with air at ambient temperature without any application of energy, or
- solid substances and preparations which may readily catch fire after brief contact with a source of ignition and which continue to burn or to be consumed after removal of the source of ignition, or
- liquid substances and preparations having a flash point below 21 °C, or
- gaseous substances and preparations which are flammable in air at normal pressure, or
- substances and preparations which, in contact with water or damp air, evolve highly flammable gases in dangerous quantities;

(e) flammable:
liquid substances and preparations having a flash point equal to or greater than 21 °C and less than or equal to 55 °C;

(f) very toxic:
substances and preparations which, if they are inhaled or ingested or if they penetrate the skin, may involve extremely serious, acute or chronic health risks and even death;

(g) toxic:
substances and preparations which, if they are inhaled or ingested or if they penetrate the skin, may involve serious, acute or chronic health risks and even death;

(h) harmful:
substances and preparations which, if they are inhaled or ingested or if they penetrate the skin, may involve limited health risks;

(i) corrosive:
substances and preparations which may, on contact with living tissues, destroy them;

(j) irritant:
non-corrosive substances and preparations which, through immediate, prolonged or repeated contact with the skin or mucous membrane, can cause inflammation;

(k) dangerous for the environment:
substances and preparations the use of which presents or may present immediate or delayed risks for the environment;

(l) carcinogenic:
substances or preparations which, if they are inhaled or ingested or if they penetrate the skin, may induce cancer in man or increase its incidence;

(m) teratogenic;

(n) mutagenic.

Article 3

1. The physico-chemical properties of the substances and preparations shall be determined according to the methods specified in Annex V (A); their toxicity shall be determined according to the methods specified in Annex V (B) and their ecotoxicity according to those specified in Annex V (C).

2. The real or potential environmental hazard shall be assessed according to the characteristics set out in Annexes VII and VIII, on the basis of any existing internationally recognized parameters.

3. The general principles of the classification and labelling of substances and preparations shall be applied according to the criteria in Annex VI, save where contrary requirements for dangerous preparations are specified in separate Directives.

Article 4

1. The classification of dangerous substances according to the degree of hazard and to the specific nature of the risks involved shall be based on the categories laid down in Article 2 (2). For categories (a) to (j) the substances shall be classified according to the greatest degree of hazard, in accordance with Article 16 (4).

2. The dangerous substances listed in Annex I shall, where appropriate, be given a rating enabling the health hazard of preparations to be assessed. The ratings shall be determined in accordance with the criteria established by a subsequent Council Directive.

Article 5

1. The Member Sates shall take all the measures necessary to ensure that without prejudice to Article 8 substances cannot be placed on the market on their own or in preparations unless the substances have been:
- notified to the competent authority of one of the Member States in accordance with this Directive,
- packaged and labelled in accordance with Articles 15 to 18 and with the criteria in Annex VI, and in accordance with the results of the tests provided for in Article 6.

2. The measures referred to in the second indent of paragraph 1 shall apply until the substance is listed in Annex I or until a decision not to list it has been taken in accordance with the procedure laid down in Article 21.

Dangerous substances not yet appearing in Annex I but included in the list referred to in Article 13 (1) or already on the market before 18 September 1981 must, in so far as the manufacturer whether or not established in the Community may reasonably be expected to be aware of their dangerous properties, be packaged and provisionally labelled by the manufacturer or his representative in accordance with the rules laid down in Articles 15 to 18 and with the criteria in Annex VI.

Article 6

1. Without prejudice to Articles 1 (4) and 8 (1), any manufacturer or importer into the Community of a substance within the meaning of this Directive shall be required to submit to the competent authority referred to in Article 7 of the Member State in which the substance is produced or into which it is imported into the Community, at the latest 45 days before the substance is placed on the market, a notification including:

— a technical dossier supplying the information necessary for evaluating the foreseeable risks, whether immediate or delayed, which the substance may entail for man and the environment, and containing at least the information and results of the studies referred to in Annex VII, together with a detailed and full description of the studies conducted and of the methods used or a bibliographical reference to them,

— a declaration concerning the unfavourable effects of the substance in terms of the various uses envisaged,

— the proposed classification and labelling of the substance in accordance with this Directive,

— proposals for any recommended precautions relating to the safe use of the substance.

2. However, in the case of a substance which has already been notified, the competent authority may agree that the notifier of that substance may, for the purposes of the technical dossier, refer to the results of the studies carried out by one or more previous notifiers, provided the latter have given their agreement in writing.

3. If a substance is already listed in Annex I, the notifier need not present the declaration concerning its unfavourable effects, the proposed classification and the proposals for any recommended precautions relating to safe use. Furthermore, the notifier need not supply the information required for the technical dossier in Annex VII, with the exception of points 1 and 2 of that Annex, if the substance was originally notified at least 10 years previously.

4. Any notifier of a substance already notified shall be required to inform the competent authority of:

— changes in the annual or total quantities placed on the market by him in accordance with the tonnage range laid down in Annex VII, point 2.2.1,

— new knowledge of the effects of the substance on man and/or the environment of which he may reasonably be expected to have become aware,

— new uses for which the substance is placed on the market (within the meaning of Annex VII, point 2.1.2) of which he may reasonably be expected to have become aware,

— any change in the properties resulting from a modification of the substance referred to in Annex VII, point 1.3.

5. The notifier shall also be required to inform the competent authority of the results of the studies carried out in accordance with Annex VIII.

Article 7

1. Member States shall appoint the competent authority or authorities responsible for receiving the information provided for in Article 6 and examining its conformity with the requirements of the Directive, and in particular:

— the notifier's proposed findings on any foreseeable risks which the substance may entail,

— classification and labelling,

— the proposals for any recommended precautions relating to safe use submitted by the notifier.

Moreover, if it can be shown to be necessary for the evaluation of the hazard which may be caused by a substance, the competent authorities may:

— ask for further information and/or verification tests concerning the substances of which they have been notified; this may also include requesting the information referred to in Annex VIII earlier than provided for therein,

— carry out such sampling as is necessary for control purposes,

— take appropriate measures relating to safe use of a substance pending the introduction of Community provisions.

2. The procedure laid down in Article 21 shall be followed in confirming or amending proposals for:

— classification,

— labelling, and

— the recommended precautionary measures provided for in Annex VII, points 2.3, 2.4 and 2.5.

3. Member States and the Commission shall ensure that any information concerning commercial exploitation or manufacturing is kept secret.

Article 8

1. The substances listed below, shall be considered as having been notified within the meaning of this Directive when the following conditions are fulfilled:

— polymerizates, polycondensates and polyadducts except those containing in combined form 2% or more of any monomer unmarketed before 18 September 1981,

— substances for research and analysis purposes, in so far as they are placed on the market for the purpose of determining their properties in accordance with this Directive;

— substances placed on the market for research or analysis purposes in quantities of less than one tonne per year per manufacturer or importer and intended solely for laboratories,

— substances placed on the market in quantities of less than one tonne per year per manufacturer provided that the manufacturer announces their identity, labelling data and quantity to the competent authorities of the Member States where the substances are placed on the market and complies with any conditions imposed by those authorities.

However, substances placed on the market at the research and development stage with a limited number of registered customers, in quantities which are limited to the purpose of the research and development but which amount to more than one tonne per year per manufacturer, shall qualify for exemption for a period of one year, provided that the manufacturer announces their identity, labelling data and quantity to the competent authorities of each Member State where the manufacture, research or development takes place and complies with any conditions imposed by those authorities on such research and development; after this period, these substances shall be subject to notification. The manufacturer shall also give an assurance that the substance or the preparation in which it is incorporated will be handled by customers' staff only, under controlled conditions, and will not be made available to the public.

2. The substances referred to in paragraph 1 must, in so far as the manufacturer may reasonably be expected to be aware of their dangerous properties, be packaged and provisionally labelled by the manufacturer or his representative in accordance with the rules laid down in Articles 15 to 18 and with the criteria imposed in Annex VI.

If labelling in accordance with the principles set out in Article 16 is not yet possible, the label should bear the warning: "Caution — substance not yet fully tested".

3. Where a substance as referred to in paragraph 1, labelled in accordance with the principles set out in Article 16, is very toxic or toxic, the manufacturer or importer of such a substance must transmit to the competent authority any appropriate information as regards Annex VII, points 2.3, 2.4 and 2.5.

Article 9

When a Member State has received the notification dossier or additional information referred to in Article 6 it shall forthwith send to the Commission a copy of the dossier or a summary thereof together with any relevant comments; in the case of the further information referred to in Article 7 (1) and the additional information or studies provided for in Annex VIII, the competent authority shall notify the Commission of the tests chosen, the reasons for their choice, and the assessment of their results.

Article 10

1. On receipt of the copy of the notification dossier, the summary thereof or the additional information sent by a Member State, the Commission shall forward:

— the notification dossier or the summary thereof to the other Member States,

— any other relevant information it has collected pursuant to this Directive to all Member States.

2. The competent authority of any Member State may consult direct the competent authority which received the original notification, or the Commission, on specific details of the data

contained in the dossier required under this Directive; it may also suggest that further tests or information be requested. If the competent authority which received the original notification fails to comply with the suggestions of other authorities regarding further information or amendments in the study programmes provided for in Annex VIII, it shall give its reasons to the other authorities concerned. Should it not be possible for the authorities concerned to reach agreement and should any one authority feel, on the basis of detailed reasons, that additional information or amendments in the study programmes are nevertheless really necessary to protect man and the environment, it may ask the Commission to take a decision in accordance with the procedure laid down in Article 21.

Article 11

1. If he considers that there is a confidentiality problem, the notifier may indicate the information provided for in Article 6 which he considers to be commercially sensitive and disclosure of which might harm him industrially or commercially, and which he therefore wishes to be kept secret from all persons other than the competent authorities and the Commission. Full justification must be given in such cases.

Industrial and commercial secrecy shall not apply to:

— the trade name of the substance,

— physico-chemical data concerning the substance in connection with Annex VII, point 3,

— the possible ways of rendering the substance harmless,

— the interpretation of the toxicological and ecotoxicological tests and the name of the body responsible for the tests,

— the recommended methods and precautions referred to in Annex VII, point 2.3 and the emergency measures referred to in Annex VII, points 2.4 and 2.5.

If the notifier himself subsequently discloses previously confidential information, he shall be required to inform the competent authority accordingly.

2. The authority receiving the notification shall decide on its own responsibility which information is covered by industrial and commercial secrecy in accordance with paragraph 1.

3. The name of a substance appearing in the list provided for in Article 13 (2) may be included in encoded form where the competent authority to which the notification has been submitted so requests because of the confidentiality problems to which publication of the name of the substance would give rise, provided that the substance is not classified as dangerous.

A substance may be included in the list in encoded form for no longer than three years.

4. Confidential information brought to the attention either of the Commission or of a Member State shall be kept secret.

In all cases such information

— may be brought to the attention only of the authorities whose responsibilities are specified in Article 7 (1),

— may, however, when administrative or legal proceedings involving sanctions are undertaken for the purpose of controlling substances placed on the market, be divulged to persons directly involved in such proceedings.

This Article and Article 12 shall not oblige a Member State whose legislation or administrative practices impose stricter limits for the protection of industrial and commercial secrecy than those laid down in these Articles to supply information, where the State concerned does not take steps to comply with these stricter limits.

Article 12

The data supplied in accordance with Articles 9 and 10 (1) may be forwarded to the Commission and the Member States in summary form.

In such cases and in the context of Article 10 (2), the competent authorities of a Member State and the Commission shall have access to the notification dossier and the additional information at all times.

Article 13

1. The Commission shall, on the basis in particular of information provided by the Member States, draw up an inventory of substances on the Community market by 18 September 1981.

In so doing it shall have regard to Articles 1 (4) and 8.

The inventory shall give the chemical name under an internationally recognized chemical

nomenclature (preferably IUPAC), the CAS number and the common name or ISO abbreviation, if any.

2. The Commission shall keep a list of all substances notified under this Directive.

3. The information and the form in which it is recorded in the list and the inventory, together with the criteria covering the provision to the Commission by the Member States of information relating to the inventory, shall be determined in accordance with the procedure laid down in Article 21.

Article 14

Annex I contains the list of substances classified in accordance with Article 4 and any recommendations relating to safe use.

Article 15

1. Member States shall take all necessary measures to ensure that dangerous substances cannot be placed on the market unless their packaging satisfies the following requirements:

(a) it shall be so designed and constructed that its contents cannot escape; this requirement shall not apply where special safety devices are prescribed;

(b) the materials constituting the packaging and fastenings must not be susceptible to adverse attack by the contents, or liable to form harmful or dangerous compounds with the contents;

(c) packaging and fastenings must be strong and solid throughout to ensure that they will not loosen and will safely meet the normal stresses and strains of handling;

(d) containers fitted with replaceable fastening devices shall be so designed that the packaging can be repeatedly refastened without the contents escaping.

2. The Member States may also prescribe that:

— packages shall initially be closed with a seal in such a way that when the package is opened for the first time the seal is irreparably damaged,

— containers with a capacity not exceeding three litres which contain dangerous substances intended for domestic use shall have child-resistant fastenings,

— containers with a capacity not exceeding one litre which contain very toxic, toxic or corrosive liquids intended for domestic use shall carry a tactile warning of danger.

3. Any technical specifications which may be necessary with regard to the devices referred to in paragraph 2 shall be adopted by the procedure in Article 21 and shall be given in Annex IX, in particular:

— in Annex IX (A) relating to child-resistant fastenings,

— in Annex IX (B) relating to tactile warnings of danger.

Article 16

1. Member States shall take all necessary measures to ensure that dangerous substances cannot be placed on the market unless the labelling on their packaging satisfies the following requirements.

2. Every package shall show clearly and indelibly the following:

— the name of the substance,

— the origin of the substance,

— the danger symbol, when laid down, and indication of danger involved in the use of the substance,

— standard phrases indicating the special risks arising from such dangers,

— standard phrases indicating the safety advice relating to the use of the substance.

(a) The name of the substance shall be one of the terms listed in Annex I; if this is not the case the name must be given in accordance with internationally recognized nomenclature.

(b) The indication of origin shall include the name and address of the manufacturer, the distributor or the importer.

(c) The following symbols and indications of danger are to be used:
- explosive:
  an exploding bomb (E)
- oxidizing:
  a flame over a circle (O)
- extremely flammable:
  a flame (F)
- highly flammable:
  a flame (F)

— very toxic:
a skull and cross-bones (T)

— toxic:
a skull and cross-bones (T)

— harmful:
a St Andrew's cross (Xn)

— corrosive:
the symbol showing the damaging effect of an acid (C)

— irritant:
a St Andrew's cross (Xi)

The symbols must conform to those in Annex II; they shall be printed in black on an orange-yellow background.

(d) The special risks involved in using the substances shall be indicated by one or more of the standard phrases which, in accordance with the references contained in the list in Annex I, are set out in Annex III. In the case of a substance not listed in Annex I, the reference to the special risks attributed to the dangerous substances shall comply with appropriate indications given in Annex III.

The phrases "extremely flammable" or "highly flammable" need not be indicated where they repeat the wording of an indication of danger used in accordance with (c) above.

(e) The safety advice relating to the use of the substances shall be indicated by standard phrases which, in accordance with the references contained in the list in Annex I, are set out in Annex IV.

The packaging shall be accompanied by the safety advice required by the above paragraph where it is materially impossible for this to be given on the label or package itself.

In the case of a substance not listed in Annex I, the safety advice relating to the dangerous substances shall comply with appropriate indications given in Annex IV.

(f) Indications such as "non-toxic", "non-harmful" or any other similar indications must not appear on the label or packaging of substances subject to this Directive.

3. In the case of irritant, highly flammable, flammable and oxidizing substances, an indication of special risks and safety advice need not be given where the package does not contain more than 125 ml. This shall also apply in the case of the same volume of harmful substances not retailed to the general public.

4. When more than one danger symbol is assigned to a substance:

— the obligation to indicate the symbol T makes the symbols X and C optional, unless Annex I includes provision to the contrary,

— the obligation to indicate the symbol C makes the symbol X optional,

— the obligation to indicate the symbol E makes the symbols F and O optional.

Article 17

1. Where the particulars required by Article 16 appear on a label, that label shall be firmly affixed to one or more surfaces of the packaging so that these particulars can be read horizontally when the package is set down normally. The dimensions of the label shall be as follows:

Capacity of the package	*Dimensions (in millimetres)*
— not exceeding three litres:	if possible at least 52 × 74
— greater than three litres but not exceeding 50 litres:	at least 74 × 105
— greater than 50 litres but not exceeding 500 litres:	at least 105 × 148
— greater than 500 litres:	at least 148 × 210

Each symbol shall cover at least one tenth of the surface area of the label but not be less than 1 cm^2. The entire surface of the label shall adhere to the package immediately containing the substance.

These dimensions are intended solely for provision of the information required by this Directive and if necessary of any supplementary health or safety indications.

2. A label is not required where the particulars are clearly shown on the package itself, as specified in paragraph 1.

3. The colour and presentation of the label — or, in the case of paragraph 2, of the package — shall be such that the danger symbol and its background stand out clearly from it.

4. Member States may make the placing on the market of dangerous substances in their territories subject to the use of the official language or languages in respect of the labelling thereof.

5. For the purpose of this Directive, labelling requirements shall be deemed to be satisfied:

(a) in the case of an outer package containing one or more inner packages, if the outer package is labelled in accordance with international rules on the transport of dangerous substances and the inner package or packages are labelled in accordance with this Directive;

(b) in the case of a single package, if such a package is labelled in accordance with international rules on the transport of dangerous substances and with Article 16 (2) (a), (b), (d) and (e).

Where dangerous substances do not leave the territory of a Member State, labelling may be permitted which complies with national rules instead of with international rules on the transport of dangerous substances.

Article 18

1. Member States may:

(a) permit the labelling required by Article 16 to be applied in some other appropriate manner on packages which are either too small or otherwise unsuitable for labelling in accordance with Article 17 (1) and (2);

(b) by way of derogation from Articles 16 and 17 permit the packaging of dangerous substances which are neither explosive, very toxic nor toxic to be unlabelled or to be labelled in some other way if they contain such small quantities that there is no reason to fear any danger to persons handling such substances or other persons.

2. If a Member State makes use of the options provided for in paragraph 1, it shall forthwith inform the Commission thereof.

Article 19

The amendments necessary for adapting the Annexes, other than Annex VI, Part I and Annexes VII and VIII, to technical progress, shall be adopted in accordance with the procedure laid down in Article 21.

Article 20

1. A Committee (hereinafter called "the Committee") is hereby set up to adapt to technical progress the Directives concerning the elimination of technical barriers to trade in dangerous substances and preparations. It shall consist of representatives of the Member States, with a Commission representative as chairman.

2. The Committee shall adopt its own rules of procedure.

Article 21

1. Where reference is made to the procedure laid down in this Article, the matter shall be referred to the Committee by its chairman, either on his own initiative or at the request of the representative of a Member State.

2. The Commission representative shall submit a draft of the measures to be adopted to the Committee. The Committee shall give its view of the draft within a time limit set by the chairman having regard to the urgency of the matter. Decisions shall be taken by a majority of 41 votes, the votes of the Member States being weighted as provided in Article 148 (2) of the Treaty. The chairman shall not vote.

3. (a) The Commission shall adopt the proposed measures if they are in accordance with the opinion of the Committee;

(b) If the proposed measures are not in accordance with the opinion of the Committee, or if no opinion has been stated, the Commission shall without delay submit a proposal to the Council concerning the measures to be adopted. The Council shall act by a qualified majority;

(c) If the Council has not acted within three months of the proposal being submitted to it, the proposed measures shall be adopted by the Commission.

Article 22

The Member States may not, on grounds relating to notification, classification, packaging or labelling within the meaning of this Directive, prohibit, restrict or impede the placing on the market of substances which comply with the requirements of this Directive and the Annexes thereto.

Article 23

1. Where a Member State has detailed evidence that a substance, although satisfying the requirements of this Directive, constitutes a hazard for man or the environment by reason of its classification packaging or labelling, it may provisionally prohibit the sale of that substance or subject it to special conditions in its territory. It shall immediately inform the Commission and the other Member States of such action and give reasons for its decision.

2. The Commission shall consult the Member States concerned within six weeks, then give its view without delay and take the appropriate measures.

3. If the Commission considers that technical adaptations to this Directive are necessary, such adaptations shall be adopted, either by the Commission or by the Council, in accordance with the procedure laid down in Article 21; in such case, the Member State which has adopted safeguard measures may maintain them until the adaptations enter into force.'

Article 2

Articles 9, 10 and 11 of Directive 67/548/EEC hereby become Articles 24, 25 and 26.

Article 3

Annex V to Directive 67/548/EEC is hereby replaced by Annexes V to IX to this Directive.

Article 4

The following amendments shall be made to the Directives listed below:

(a) Directive 73/173/EEC:

— replace 'Article 6' by 'Article 16' in Article 5 (2) (c),

— replace 'Article 8c' by 'Article 21' in Articles 9 (2) and 10;

(b) Directive 77/728/EEC:

— replace 'Article 6' by 'Article 16' in Article 6 (2) (c),

— replace 'Article 8c' by 'Article 21' in Articles 10 (3) and 11;

(c) Directive 78/631/EEC:

— replace 'Article 6' by 'Article 16' in Article 6 (2) (g),

— replace 'Article 8c' by 'Article 21' in Articles 10 (3) and 11.

Article 5

1. No later than 18 September 1981 the Member States shall implement the laws, regulations and administrative provisions necessary to comply with Articles 1 to 4, Article 5 (1) and Articles 6 to 14 of Directive 67/548/EEC as amended by this Directive and shall inform the Commission thereof. No later than 18 September 1983 they shall implement the laws, regulations and administrative provisions necessary to comply with Article 5 (2) of Directive 67/548/EEC as amended by this Directive and shall inform the Commission thereof.

2. No later than 18 September 1981 the Member States shall adopt and publish the laws, regulations and administrative provisions necessary to comply with Articles 15 to 23 of Directive 67/548/EEC as amended by this Directive, which shall enter into force on 18 September 1981.

3. During the transitional period, when this Directive is not yet in force in certain Member States, the forwarding of the notification dossier and any other information collected by the Commission as provided for in Article 10 (1) of Directive 67/548/EEC as amended by this Directive shall be effective in the case of only those Member States in which the provisions of Articles 5 to 8 of Directive 67/548/EEC as amended by this Directive, relating to notification, are being applied.

Article 6

This Directive is addressed to the Member States.

Done at Brussels, 18 September 1979.

For the Council

The President

M. O'KENNEDY

ANNEX V

A. **METHODS FOR THE DETERMINATION OF PHYSICO-CHEMICAL PROPERTIES: for the record**

B. **METHODS FOR THE DETERMINATION OF TOXICITY: for the record**

C. **METHODS FOR THE DETERMINATION OF ECOTOXICITY: for the record**

ANNEX VI

GENERAL CLASSIFICATION AND LABELLING REQUIREMENTS FOR DANGEROUS SUBSTANCES

Part I

A. Save where otherwise provided in the separate Directives on dangerous preparations, the substances and preparations shall be classified as very toxic, toxic or harmful according to the following criteria:

(a) classification as very toxic, toxic or harmful shall be effected by determining the acute toxicity of the commercial substance or preparation in animals, expressed in LD_{50} or LC_{50} values with the following parameters being taken as reference values:

Category	LD_{50} absorbed orally in rat mg/kg	LD_{50} percutaneous absorption in rat or rabbit mg/kg	LC_{50} absorbed by inhalation in rat mg/litre/four hours
Very toxic	≤ 25	≤ 50	≤ 0·5
Toxic	25 to 200	50 to 400	0·5 to 2
Harmful	200 to 2 000	400 to 2 000	2 to 20

(b) if facts show that for the purposes of classification it is inadvisable to use the LD_{50} or LC_{50} values as a principal basis because the substances or preparations produce other effects, the substances or preparations shall be classified according to the magnitude of these effects.

Part II

B. — Corrosion criteria: for the record
— Irritation criteria: for the record

C. If the facts show the existence of effects other than the acute effects indicated by experiments with animals, e.g. carcinogenic, mutagenic, allergenic, sub-acute or chronic effects, the substances or preparations shall be classified according to the magnitude of these effects.

D. Guide for the labelling of dangerous substances and criteria for the choice of phrases allocated to dangerous substances indicating the special risks (R phrases) and the safety advice (S phrases): for the record.

ANNEX VII

INFORMATION REQUIRED FOR THE TECHNICAL DOSSIER ('BASE SET') REFERRED TO IN ARTICLE 6 (1)

When giving notification the manufacturer or any other person placing a substance on the market shall provide the information set out below.

If it is not technically possible or if it does not appear necessary to give information, the reasons shall be stated.

Tests must be conducted according to methods recognized and recommended by the competent international bodies where such recommendations exist.

The bodies carrying out the tests shall comply with the principles of good current laboratory practice.

When complete studies and the results obtained are submitted, it shall be stated that the tests were conducted using the substance to be marketed. The composition of the sample shall be indicated.

In addition, the description of the methods used or the reference to standardized or internationally recognized methods shall also be mentioned in the technical dossier, together with the name of the body or bodies responsible for carrying out the studies.

1. IDENTITY OF THE SUBSTANCE

1.1 Name

1.1.1. Names in the IUPAC nomenclature

1.1.2. Other names (usual name, trade name, abbreviation)

1.1.3. CAS number (if available)

1.2. Empirical and structural formula

1.3 Composition of the substance

1.3.1. Degree of purity (%)

1.3.2. Nature of impurities, including isomers and by-products

1.3.3. Percentage of (significant) main impurities

1.3.4. If the substance contains a stabilizing agent or an inhibitor or other additives, specify: nature, order of magnitude: ... ppm; ...%

1.3.5. Spectral data (UV, IR, NMR)

1.4. Methods of detection and determination

A full description of the methods used or the appropriate bibliographical references

2. INFORMATION ON THE SUBSTANCE

2.1. Proposed uses

2.1.1. Types of use

Describe: the function of the substance .....

the desired effects .....

2.1.2. Fields or application with approximate breakdown

(a) closed system

— industries .....

— farmers and skilled trades .....

— use by the public at large .....

(b) open system

— industries .....

— farmers and skilled trades .....

— use by the public at large .....

2.2. Estimated production and/or imports for each of the anticipated uses or fields of application

2.2.1. Overall production and/or imports in order of tonnes per year 1; 10; 50; 100; 500; 1 000 and 5 000

— first 12 months .....tonnes/year

— thereafter .....tonnes/year

2.2.2. Production and/or imports, broken down in accordance with 2.1.1 and 2.1.2, expressed as a percentage

— first 12 months .....

— thereafter .....

2.3. Recommended methods and precautions concerning:

2.3.1. handling .....

2.3.2. storage .....

2.3.3. transport .....

2.3.4. fire (nature of combustion gases or pyrolysis, where proposed uses justify this)

2.3.5. other dangers, particularly chemical reaction with water

2.4. Emergency measures in the case of accidental spillage

2.5. Emergency measures in the case of injury to persons (e.g. poisoning)

3. PHYSICO-CHEMICAL PROPERTIES OF THE SUBSTANCE

3.1. Melting point

.....°C

3.2. Boiling point

..... °C ..... Pa

3.3. Relative density

..... (D_4^{20})

3.4. Vapour pressure

..... Pa at ..... °C

..... Pa at ..... °C

3.5. Surface tension

..... M/m (..... °C)

3.6. Water solubility

..... mg/litre (..... °C)

3.7. Fat solubility

Solvent — oil (to be specified)

..... mg/100 g solvent (..... °C)

3.8. Partition coefficient

n-octanol/water

3.9. Flash point

..... °C ☐ open cup ☐ closed cup

3.10. Flammability (within the meaning of the definition given in Article 2 (2) (c), (d) and (e))

3.11. Explosive properties (within the meaning of the definition given in Article 2 (2) (a))

3.12. Auto-flammability

..... °C

3.13. Oxidizing properties (within the meaning of the definition given in Article 2 (2) (b))

4. TOXICOLOGICAL STUDIES

4.1. Acute toxicity

4.1.1. Administered orally

LD_{50}..... mg/kg

Effects observed, including in the organs .....

4.1.2. Administered by inhalation

LC_{50}..... (ppm) Duration of exposure .....hours

Effects observed, including in the organs .....

4.1.3. Administered cutaneously (percutaneous absorption)

LD_{50}..... mg/kg

Effects observed, including in the organs .....

4.1.4. Substances other than gases shall be administered via two routes at least, one of which should be the oral route. The other route will depend on the intended use and on the physical properties of the substance.

Gases and volatile liquids should be administered by inhalation (a minimum period of administration of four hours).

In all cases, observation of the animals should be carried out for at least 14 days.

Unless there are contra-indications, the rat is the preferred species for oral and inhalation experiments.

The experiments in 4.1.1, 4.1.2 and 4.1.3 shall be carried out on both male and female subjects.

4.1.5. Skin irritation

The substance should be applied to the shaved skin of an animal, preferably an albino rabbit.

Duration of exposure ..... hours

4.1.6. Eye irritation

The rabbit is the preferred animal.

Duration of exposure ..... hours

4.1.7. Skin sensitization

To be determined by a recognized method using a guinea-pig.

4.2. Sub-acute toxicity

4.2.1. Sub-acute toxicity (28 days)

Effects observed on the animal and organs according to the concentrations used, including clinical and laboratory investigations .....

Dose for which no toxic effect is observed .....

4.2.2. A period of daily administration (five to seven days per week) for at least four weeks should be chosen. The route of administration should be the most appropriate having regard to the intended use, the acute toxicity and the physical and chemical properties of the substance.

Unless there are contra-indications, the rat is the preferred species for oral and inhalation experiments.

4.3. Other effects

4.3.1. Mutagenicity (including carcinogenic pre-screening test)

4.3.2. The substance should be examined during a series of two tests, one of which should be bacteriological, with and without metabolic activation, and one non-bacteriological.

5. ECOTOXICOLOGICAL STUDIES

5.1. Effects on organisms

5.1.1. Acute toxicity for fish

LC_{50}..... (ppm) Duration of exposure determined in accordance with Annex V (C)

Species selected (one or more) .....

5.1.2. Acute toxicity for daphnia

LC_{50}..... (ppm) Duration of exposure determined in accordance with Annex V (C)

5.2. Degradation

— biotic

— abiotic

The BOD and the BOD/COD ratio should be determined as a minimum

6. POSSIBILITY OF RENDERING THE SUBSTANCE HARMLESS

6.1. For industry/skilled trades

6.1.1. Possibility of recovery .....

6.1.2. Possibility of neutralization .....

6.1.3. Possibility of destruction:

— controlled discharge .....

— incineration .....

— water purification station .....

— others .....

6.2. For the public at large

6.2.1. Possibility of recovery .....

6.2.2. Possibility of neutralization .....

6.2.3. Possibility of destruction:

— controlled discharge .....

— incineration .....

— water purification station .....

— others .....

ANNEX VIII

ADDITIONAL INFORMATION AND TESTS REQUIRED UNDER ARTICLE 6 (5)

Any person who has notified a substance to a competent authority in accordance with the requirements of Article 6 of this Directive shall provide at the request of the authority further information and carry out additional tests as provided for in this Annex.

If it is not technically possible or if it does not appear necessary to give information, the reasons shall be stated.

Tests shall be conducted according to methods recognized and recommended by the competent international bodies where such recommendations exist.

The bodies carrying out the tests shall comply with the principles of good current laboratory practice.

When complete studies and the results obtained are submitted, it shall be stated that the tests were conducted using the substance marketed. The composition of the sample shall be indicated.

In addition the description of the methods used or the reference to standardized or internationally recognized methods shall also be mentioned in the technical dossier, together with the name of the body or bodies responsible for carrying out the studies.

LEVEL 1

Taking into account:

— current knowledge of the substance,

— known and planned uses,

— the results of the tests carried out in the context of the base set,

the competent authority may require the following additional studies where the quantity of a substance placed on the market by a notifier reaches a level of 10 tonnes per year or a total of 50 tonnes and if the conditions specified after each of the tests are fulfilled in the case of that substance.

Toxicological studies

— Fertility study (one species, one generation, male and female, most appropriate route of administration)

If there are equivocal findings in the first generation, study of a second generation is required.

It is also possible in this study to obtain evidence on teratogenicity.

If there are indications of teratogenicity, full evaluation of teratogenic potential may require a study in a second species.

— Teratology study (one species, most appropriate route of administration)

This study is required if teratogenicity has not been examined or evaluated in the preceding fertility study.

— Sub-chronic and/or chronic toxicity study, including special studies (one species, male and female, most appropriate route of administration)

If the results of the sub-acute study in Annex VII or other relevant information demonstrate the need for further investigation, this may take the form of a more detailed examination of certain effects, or more prolonged exposure, e.g. 90 days or longer (even up to two years).

The effects which would indicate the need for such a study could include for example:

(a) serious or irreversible lesions;

(b) a very low or absence of a 'no effect' level;

(c) a clear relationship in chemical structure between the substance being studied and other substances which have been proved dangerous.

— Additional mutagenesis studies (including screening for carcinogenesis)

A. If results of the mutagenesis tests are negative, a test to verify mutagenesis and a test to verify carcinogenesis screening are obligatory.

If the results of the mutagenesis verification test are also negative, further mutagenesis tests are not necessary at this level; if the results are positive, further mutagenesis tests are to be carried out (see B).

If the results of the carcinogenesis screening verification test are also negative, further carcinogenesis screening verification tests are not necessary at this level; if the results are positive further carcinogenesis screening verification tests are to be carried out (see B).

B. If the results of the mutagenesis tests are positive (a single positive test means positive), at least two verification tests are necessary at this level. Both mutagenesis tests and carcinogenesis screening tests should be considered here. A positive result of a carcinogenesis screening test should lead to a carcinogenesis study at this level.

Ecotoxicology studies

— An algal test: one species, growth inhibition test.

— Prolonged toxicity study with Daphina magna (21 days, thus study should also include determination of the 'no-effect level' for reproduction and the 'no-effect level' for lethality).

The conditions under which this test is carried out shall be determined in accordance with the procedure described in Article 21 in the light of the methods laid down in Annex V (C) for acute toxicity tests with Daphnia.

— Test on a higher plant.

— Test on an earthworm.

— Prolonged toxicity study with fish (e.g. Oryzias, Jordanella, etc.; at least a period of 14 days; thus study should also include determination of the 'threshold level').

The conditions under which this test is carried out shall be determined in accordance with the procedure described in Article 21 in the light of the methods adopted under Annex V (C) for acute toxicity tests with fish.

— Tests for species accumulation; one species, preferably fish (e.g. Poecilla reticulata).

— Prolonged biodegradation study, if sufficient (bio)degradation has not been proved by the studies laid down in Annex VII, another test (dynamic) shall be chosen with lower concentrations and with a different inoculum (e.g. flow-through system).

In any case, the notifier shall inform the competent authority if the quantity of a substance placed on the market reaches a level of 100 tonnes per year or a total of 500 tonnes.

On receipt of such notification and if the requisite conditions are fulfilled, the competent authority, within a time limit it will determine, shall require the above tests to be carried out unless in any particular case an alternative scientific study would be preferable.

LEVEL 2

If the quantity of a substance placed on the market by a notifier reaches 1 000 tonnes per year or a total of 5 000 tonnes, the notifier shall inform the competent authority. The latter shall then draw up a programme of tests to be carried out by the notifier in order to enable the competent authority to evaluate the risks of the substance for man and the environment.

The test programme shall cover the following aspects unless there are strong reasons to the contrary, supported by evidence, that it should not be followed:

— chronic toxicity study,

— carcinogenicity study,

— fertility study (e.g. three-generation study); only if an effect on fertility has been established at level 1,

— teratology study (non-rodent species) study to verify teratology study at level 1 and experiment additional to the level 1 study, if effects on embryos/foetuses have been established,

— acute and sub-acute toxicity study on second species: only if results of level 1 studies indicate a need for this. Also results of biotransformation studies and studies on pharmacokinetics may lead to such studies,

— additional toxicokinetic studies.

Ecotoxicology

— Additional tests for accumulation, degradation and mobility.

The purpose of this study should be to determine any accumulation in the food chain.

For further bioaccumulation studies special attention should be paid to the solubility of the substance in water and to its n-octanol/water partition coefficient.

The results of the level 1 accumulation study and the physiocochemical properties may lead to a large-scale flow-through test.

— Prolonged toxicity study with fish (including reproduction).

— Additional toxicity study (acute and sub-acute) with birds (e.g. quails): if accumulation factor is greater than 100.

— Additional toxicity study with other organisms (if this proves necessary).

— Absorption — desorption study where the substance is not particularly degradable.

ANNEX IX

A. PROVISIONS RELATING TO CHILD-RESISTANT FASTENINGS: for the record

B. PROVISIONS RELATING TO TACTILE WARNINGS OF DANGER: for the record

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SUMMARY OF NOTIFICATION DOSSIER OF A NEW CHEMICAL SUBSTANCE

In accordance with Directive 79/831/EEC (Article 9)

O.J. L 259, volume 22, 15 October 1979

1. Details of the Notification

Member State of notification:

Notification number:

Name of the substance (Trade name or other identification name if the trade name is not available):

Date of notification:

This substance has already been notified under No.
(Lead number first, followed by all previous notification numbers):

2. Notifier/Manufacturer/Importer

NOTIFIER (Name and address):

Domestic manufacturer ¦__¦ *Importer* ¦__¦

In case of import:
Manufacturer (Name and address)

3. *Name to be included in ELINCS*

The view of the authority with regard to the publication of the trade name/IUPAC name is as follows:

Non-Dangerous Substances		*Dangerous Substances*	
The IUPAC name and trade name	☐ *(A)*	*The IUPAC name and trade name*	☐ *(D)*
Only the trade name for a period of .... years (maximum 3)	☐ *(B)*	*Only the trade name until such time as the substance is added to Annex 1 of the Directive*	☐ *(E)*
The trade name only for an indefinite period for reasons of commercial secrecy	☐ *(C)*		

4. *Classification and Labelling*

Lead competent authorities should state their formal proposal for classification and labelling with justification (where necessary)

Classification

- ☐ *very toxic*
- ☐ *toxic*
- ☐ *harmful*
- ☐ *corrosive*
- ☐ *irritant*
- ☐ *explosive*
- ☐ *oxidising*
- ☐ *extremely flammable*
- ☐ *highly flammable*
- ☐ *flammable*
- ☐ *carcinogenic*
- ☐ *teratogenic*
- ☐ *mutagenic*
- ☐ *or otherwise dangerous to man or the environment*
- ☐ *not classified*

Labelling

Symbol(s) and indication of danger(s) (In accordance with Annex II of Directive 67/548/EEC)

Risk phrases (In accordance with Annex III of Directive 67/548/EEC)

Safety phrases (In accordance with Annex IV of Directive 67/548/EEC)

5. *Comments/Observations of the Competent Authority concerning the Notification (including the competent authority's acceptance of, or comments on the notifier's proposed classification and labelling (page 52).*

6. *The following summary of the notification of a new chemical substance is transmitted to the Commission of the European Communities in accordance with Article 9 of Directive 79/831/EEC by .....*
(member state)

There are ... annexes attached to this summary notification. They are numbered in accordance with the corresponding entry number in this summary. The items which the notifier wishes to have considered as confidential and have been accepted as confidential by the competent Authority are properly marked in this summary.

The competent Authority accepts the reasons given by the notifier for not supplying certain information in accordance with the preamble to Annex VII of Directive 79/831/EEC (comments are given where necessary).

Signature: .....

Name and position of the responsible Official(s):

Signature: .....

Name and position of the responsible Official(s):

SUMMARY NOTIFICATION DOSSIER FOR SUBSTANCES NOTIFIED IN CONFORMITY WITH ARTICLE 6.1 OF DIRECTIVE 79/831/EEC ON THE CLASSIFICATION, PACKAGING AND LABELLING OF DANGEROUS SUBSTANCES

This summary notification dossier is divided into four sections.

A. Technical dossier supplying the information necessary for evaluating the foreseeable risks, whether immediate or delayed, which the substance may entail for man and the environment;

B. Declaration concerning the unfavourable effects of the substance in terms of the various uses envisaged;

C. Proposed classification and labelling of the substance in accordance with the directive;

D. Proposals for any recommended precautions relating to the safe use of the substance.

When information is confidential, tick appropriate block. Where this block is absent or hatchered, confidentiality cannot be claimed for the corresponding data.

1.1 Name

001

1.1.1 Names in the IUPAC nomenclature

Confidential

English	

1.1.2 Other names

- Trade name(s) (or other public identifier(s)):	/// /// ///
- Other names:	

1.1.3 CAS number (if available, otherwise enter "Not yet allocated")

1.2. Empirical and structural formula

empirical formula (according to the Hill system, and the CAS system if different from Hill) Hill: CAS:	
structural formula (if this formula cannot be given, please comment)	

1.3 Composition of the substance

1.3.1 Degree of purity (percentage by weight)

Confidential

typical concentration	lower limit	upper limit		

(Concentration of the individual components if the substance is a complex reaction mixture)

1.3.2/1.3.3 Identity and percentage of impurities, including isomers and by-products

Confidential

IUPAC name, CAS number if available and percentage by weight of significant impurities (lower/upper limit)	%		

1.3.4 Essential additives (stabilizing agents, inhibitors, other additives):

Confidential

IUPAC name, CAS number if available, and mean percentage by weight (lower/upper limit) and functions	ppm or %		

003

1.3.5 Spectral data

Confidential

UV/visible spectrum: (Annex ...) IR Spectrum: (Annex ...) NMR Spectrum: (Annex ...) Others (eg Mass spectrum) (Annex ...)	

1.4 Methods of detection and determination.

004

A brief description of the methods used to detect and determine the substances detailed under 1.1.1, 1.3.1, 1.3.3 and 1.3.4 or the appropriate bibliographical references.

Confidential

Substance(s) determined	Method	

2.1 PROPOSED USES

005

2.1.1 Types of use

Confidential

Use category:	
Desired effects:	
Detailed information on envisaged uses:	

Form in which the notifier intends to place the substance on the market

☐ substance as such ☐ substance in a preparation	
Trade name of the preparation(s):	
Nature of the preparation(s) (granulate, paste.....):	
Estimated maximum content of the substance in the preparation(s):	

2.1.2 *Fields of application with approximate breakdown (e.g. Industry, open system, 100%)*

Industry, Closed Systems,	%	
Industry, Open Systems,	%	
Farmers and Skilled Trades, Closed Systems,	%	
Farmers and Skilled Trades, Open Systems,	%	
Public at large, Closed Systems,	%	
Public at large, Open Systems,	%	

037

2.2 ESTIMATED PRODUCTION IN AND/OR IMPORTS TO THE MEMBER STATE FOR EACH USE AND FOR EACH FIELD OF APPLICATION (In tonnes per calendar year)

Confidential

2.2.1 PRODUCTION AND/OR IMPORTS

Production ☐ Import ☐

2.2.1.1 For the balance of the calendar year of notification:

..... tonnes

2.2.1.2 For the next three years, estimated production or imports in tonnes per calendar year

19 .. :

19 .. :

19 .. :

2.2.2 Production and/or imports broken down (In accordance with 2.1.1 and 2.1.2)

2.3 Recommended methods and precautions concerning*

2.3.1 Handling

2.3.2 Storage

2.3.3. Transport (including international and national code number for transport, eg UN, if available)

2.3.4 *Fire (including nature of combustion gases or pyrolysis)*

Recommended extinguishing agents:

Products arising from burning or pyrolysis:*

Protective equipment:

2.3.5 *Other dangers, particularly reaction with water*

other dangers

chemical reaction in combination with water

* *Indicate if this information derives from tests carried out on the substance.*

011

2.6 Composition of the tested substance

Exact composition of the samples which were used to perform the tests in 3.1 to 5.3 (the purity must be within the ranges given in sections 1.3.1 - 1.3.4).

Batch No.	Used for tests:	Composition (1.3)

It is much to be preferred that all tests are conducted on the same batch. However, where several batches are used the appropriate batch number should be indicated for each test; where only one batch is described above it will be assumed unless indicated to the contrary that all tests were conducted on this batch.

2.4 *Emergency measures in the case of accidental spillage*

010

2.5 *Emergency measures in the case of injury to persons (e.g. poisoning) (First-aid measures, recommended treatment)*

Eyes:

Skin:

Ingestion:

Inhalation:

012

3.0 Nature of the substance

1. Colour -

2. Physical state at 20°C and 101.3 kPa

☐ solid ☐ liquid ☐ gaseous

3. State (e.g. powder, viscous, crystalline, compact, particle size)

(Where the particle size distribution has been determined, it should been given here and details of the test should be given under item 3.14)

3.1 Melting temperature/Freezing temperature

... °C

Method:

Body responsible for test:

Comments:

3.2 Boiling temperature

... °C at 101.3 kPa.

Method:

Body responsible for test:

Comments:

3.3 Relative density

D_4^{20}

Method:

Body responsible for test:

Comments:

3.4 Vapour pressure

... Pa at ... °C
... Pa at ... °C
... Pa at ... °C (20 or 25°C) (estimated from data above)

Method:

Body responsible for test:

Comments:

3.5 Surface tension (of aqueous solution)

mN/m at °C	Concentration mg/l
Method	
Body responsible for test:	
Comments:	

3.6 Water solubility

mg/l at °C at pH ...(if available)
Method:
Analytical method:
Body responsible for test:
Comments:

015

3.7 Fat solubility

... mg/100 g solvent at ... °C

Method:

Analytical method:

Body responsible for test:

Comments:

3.8 Partition coefficient n-octanol/water

log Pow = at ... °C

Method:

Analytical method:

Body responsible for test:

Comments:

016

3.9 Flash point

... °C; open cup ☐ ; closed cup ☐
Method (including reference to the specific procedure used)
Body responsible for test:
Comments:

017

3.10 Flammability (within the meaning of the definition given in article 2 (2) (c), (d) and (e))

extremely flammable (Test Methods A9 / A2 in Annex V)	☐ yes	☐ no
highly flammable	☐ yes	☐ no
- pyrophoric substance (A 13)	☐ yes	☐ no
- highly flammable solid substance (A 10)	☐ yes	☐ no
- highly flammable liquid substance (A 9)	☐ yes	☐ no
- highly flammable gas (A 11)	☐ yes	☐ no
- in contact with water or humid air, substance evolves highly flammable gases in dangerous quantities (A12)	☐ yes	☐ no
flammable (A9)	☐ yes	☐ no

Method(s):

Body responsible for test:

Comments:

3.11 *Explosive properties (within the meaning of the definition given in article 2 (2) (a))*

explosive under influence of a flame:	☐ yes	☐ no
more sensitive to shocks than m-dinitrobenzene:	☐ yes	☐ no
more sensitive to friction than m-dinitrobenzene:	☐ yes	☐ no

Method:

Body responsible for test:

Comments:

3.12 *Auto-flammability*

- *Self ignition temperature on heating .... °C (Test Method A15 / A16 of Annex V)*

Method (including reference to the specific procedure used in the case of method A15)

Body responsible for test:

Comments:

3.13 Oxidizing properties (within the meaning of the definition given in article 2 (2) (b))

oxidizing ☐ yes ☐ no organic peroxide ☐ max. burning rate of test mixture : ..... mm/s max. burning rate of reference mixture : ..... mm/s
Method
Body responsible for test:
Comments:

3.14 Any additional physico-chemical properties, where available

(minimum information: Property; Result; Test Method; Body responsible for the test; Comments)

4.1 Acute toxicity

4.1.1 Administered orally

On the basis of the test results given below and in conformity with the criteria given in annex VI of the Directive, the substance should be:

classified as very toxic ☐

classified as toxic ☐

classified as harmful ☐

not classified ☐

Limit test ☐ yes ☐ no

LD_{50}: mg/kg

95% confidence limits:

Slope of the dose-mortality curve:

Species/strain:

Vehicle:

Results:

	dose	number of animals	number of deaths
♂			
♀			

021

4.1.1 Administered orally (continued)

Signs of toxicity related to dose level used, time of onset and duration
Effects in organs (related to dose level):

022

Method:

Body responsible for test:

Comments:

On the basis of the test results given below and in conformity with the criteria given in annex VI of the Directive, the substance should be:

classified as very toxic ☐

classified as toxic ☐

classified as harmful ☐

not classified ☐

Limit test ☐ yes ☐ no

LC_{50}: mg/l

95% confidence limits:

Slope of the concentration-mortality curve:

Species/strain:

Exposure period: hours

Method of exposure:

Physical form of substance	gas	liq. aerosol	solid aerosol
	☐	☐	☐

Mass median aerodynamic diameter (for liquid and solid aerosols):

Vehicle:

Results:

	concentration	number of animals	number of deaths
♂			
♀			

4.1.2 Administered by inhalation (continued)

Signs of toxicity related to concentration, time of onset and duration
Effects in organs (related to concentration):
Method:

025

4.1.2 Administered by inhalation (continued)

Body responsible for test:
Comments:

4.1.3 Administered cutaneously

On the basis of the test results given below and in conformity with the criteria given in annex VI of the Directive, the substance should be:

classified as very toxic ☐

classified as toxic ☐

classified as harmful ☐

not classified ☐

Limit test ☐ yes ☐ no

LD_{50}: mg/kg

95% confidence limits:

Slope of the dose-mortality curve:

Species/strain:

Exposure period: hours

Type of dressing:

occlusive ☐ semi-occlusive ☐

Vehicle:

Results:

	dose	number of animals	number of deaths
♂			
♀			

Signs of toxicity related to dose level used, time of onset and duration:

a) local:

b) systemic:

Effects in organs (related to dose level):

028

4.1.3 Administered cutaneously (continued)

Method:
Body responsible for test:
Comments:

029

4.1.5 Skin irritation

On the basis of the test results given below and in conformity with the criteria given in Annex VI of the Directive the substance should be:

classified as corrosive ☐

classified as irritant ☐

not classified ☐

Species/strain:

Number of animals:

Duration of exposure: hours

Amount of substance:

Type of dressing: occlusive ☐ semi-occlusive ☐

Vehicle:

Reversibility of any observed effect:

Changes fully reversible within ... days

Changes not fully reversible within an observation period of ... days

Overall results:

If 3 animals or less	* mean score animal n° 1	2	3	maximum value	maximum duration of any effect	Maximum value at the end of the observation period
erythema/eschar						
oedema						

* calculated on the basis of the scores at 24, 48, 72 h for each animal

If > 3 animals	** mean score	maximum value	maximum duration of any effect	Maximum value at the end of the observation period
erythema/eschar				
oedema				

** calculated on the basis of the scores at 24, 48, 72 h for all animals.

4.1.5 Skin irritation (continued)

Other observations:
Method:
Body responsible for test:
Comments:

4.1.6 Eye irritation

On the basis of the test results given below and in conformity with the criteria given in Annex VI of the Directive the substance should be:

classified as irritant ☐

not classified ☐

Species/strain:

Number of animals:

Nature and amount of substance:

Reversibility of any observed effects:

Changes fully reversible within ... days

Changes not fully reversible within an observation period of ... days

Overall results:

if 3 animals or less	* mean score animal n° 1	2	3	maximum value	maximum duration of any effect	maximum value at the end of the observation period
conjunctiva/redness						
conjunctiva/chemosis						
cornea						
iris						

* calculated on the basis of the scores at 24, 48, 72 h for each animal

if > 3 animals	** mean score	maximum value	maximum duration of any effect	Maximum value at the end of the observation period
conjunctiva/redness				
conjunctiva/chemosis				
cornea				
iris				

** calculated on the basis of the scores at 24, 48, 72 h for all animals

Other observations:

Method:

Body responsible for test:

Comments:

4.1.7 Skin sensitization

On the basis of the test results given below and in conformity with the criteria given in Annex VI of the Directive the substance should be

classified as irritant ☐

not classified ☐

Species/strain:

Number of animals in test group:

Number of animals in negative control group:

Maximum concentration not giving rise to irritating effects in the preliminary test :

Concentrations of test material and vehicle used at each stage of induction :
a)

b)

Concentrations of test material and vehicle used at each challenge :
a)

b)

Signs of irritation during induction:

Results:

	Challenge concentrations of test substance (a,b,etc. if more than 1 concentration)	Number of animals showing skin reactions after			
		1st challenge		2nd challenge	
		24 hr	48 hr	24 hr	48 hr
Test group	a)				
	b)				
Negative control group	a)				
	b)				

Number of animals showing evidence of sensitization at each challenge concentration:

4.1.7 Skin sensitization (continued)

034

Other observations:
Method (type of test):
Body responsible for test:
Comments:

4.2.1 Subacute toxicity (28-day-test)

On the basis of the test results given below and in conformity with the criteria given in Annex VI of the Directive the substance should be

classified as toxic ☐

classif ied as harmful ☐

not classified ☐

Limit test yes ☐ no ☐

Dose or concentration at which no toxic effects were observed:
mg/kg/day
mg/l/...h/day

Species/strain:

Route of administration:

Method of administration or of exposure:

Vehicle:

Mass median aerodynamic diameter (for liquid and solid aerosols):

Duration of exposure per day (inhalation or dermal) : hours

Dosing regime (5 or 7 days/week):

Number of animals, doses (concentrations) and group numbers:

	Number of animals	Dose or concentration	Group number
♂			1
			2
			3
			4
			5
			6
♀			1
			2
			3
			4
			5
			6

Results (in relation to dose levels/concentrations):

1) Clinical observations:

2) Laboratory findings:

3) Effects in organs:

037

4.2.1 Subacute toxicity (28-day-test) (continued)

Dose or concentration at which no effect was observed (if available) : mg/kg/day mg/l/...h/day
Method:
Body responsible for test:
Comments:

038

4.3 Mutagenicity

4.3.1 Bacteriological test

Type of bacteria/strain:

Concentration range in the main test -
with metabolic activation:

without metabolic activation:

Concentration of test substance observed to be toxic to bacteria

a) In a preliminary test: with metabolic activation:

without metabolic activation:

b) In the main test: with metabolic activation:

without metabolic activation:

Solvent:

Concentration of the test substance resulting in precipitation:

Metabolic activation system:

Observations:

Result:	+	-
With metabolic activation	☐	☐
Without metabolic activation	☐	☐

4.3.1 Bacteriological test (continued)

Method (type of test):

Body responsible for the test:

Comments:

4.3.2 Non-bacteriological test in vitro

Type of cell used:

Concentration range in the main test -
with metabolic activation:

without metabolic activation:

Concentrations producing toxicity:
a) In a preliminary test: with metabolic activation:

without metabolic activation:

b) In the main test : with metabolic activation:

without metabolic activation:

Vehicle:

Exposure period: with metabolic activation:

without metabolic activation:

Fixation time:

Metabolic activation system:

4.3.2 Non-bacteriological test in vitro (continued)

Observations:		
Result:	+	-
With metabolic activation	☐	☐
Without metabolic activation	☐	☐
Method (type of test)		
Body responsible for the test:		
Comments:		

4.3.3 Non-bacteriological test in vivo

Species/strain:
Dose levels:
Doses producing toxicity:
Number of animals at each dose level for each sacrifice time:
Route of administration:
Vehicle:
Sacrifice times (in hours):

4.3.3 Non-bacteriological test in vivo (continued)

Observations:

Result: + ☐ - ☐

Method (type of test)

Body responsible for the test:

Comments:

4.4 Additional toxicological tests

Minimum information: End point investigated; Description of the essential features of the test methods; Results; Test procedure used; Body responsible for the test; Comments.

042

5.1 Effects on organisms

5.1.1 Acute toxicity for fish

Values in mg l^{-1}

	24h	48h	72h	96h
LC_{50}				

No observed effect concentration at 96h ..... mg/l

Species:

static test ☐ semi-static test ☐ flow-through test ☐

% loss in concentration of the test substance over test period:

Identity and concentration of any auxiliary solvent or details of any other method used for dispersal:

Water hardness:

Method (type of test):

Body responsible for the test:

Comments:

043

5.1.2 Acute toxicity for daphnia

Conc. in mg l^{-1}

	24h	48h
EC_{50}		

No observed effect concentration after 48h ..... mg/l

Species: Daphnia magna ☐ Daphnia pulex ☐

% loss in concentration over test period:

Identity and concentration of any auxiliary solvent or details of any other method used for dispersal:

Water hardness:

Method (type of test):

Body responsible for the test:

Comments:

5.2 Degradation

5.2.0 Inhibition of microbial activity (if available)

Type of test: aerobic ☐

anaerobic ☐

Duration of test : hours

IC_{50} at hours = mg/l

No observed effect concentration at .... hours = ... mg/l

Method (type of test):

Body responsible for the test:

Comments:

5.2.1 Biodegradability

5.2.1.1 Ready biodegradability

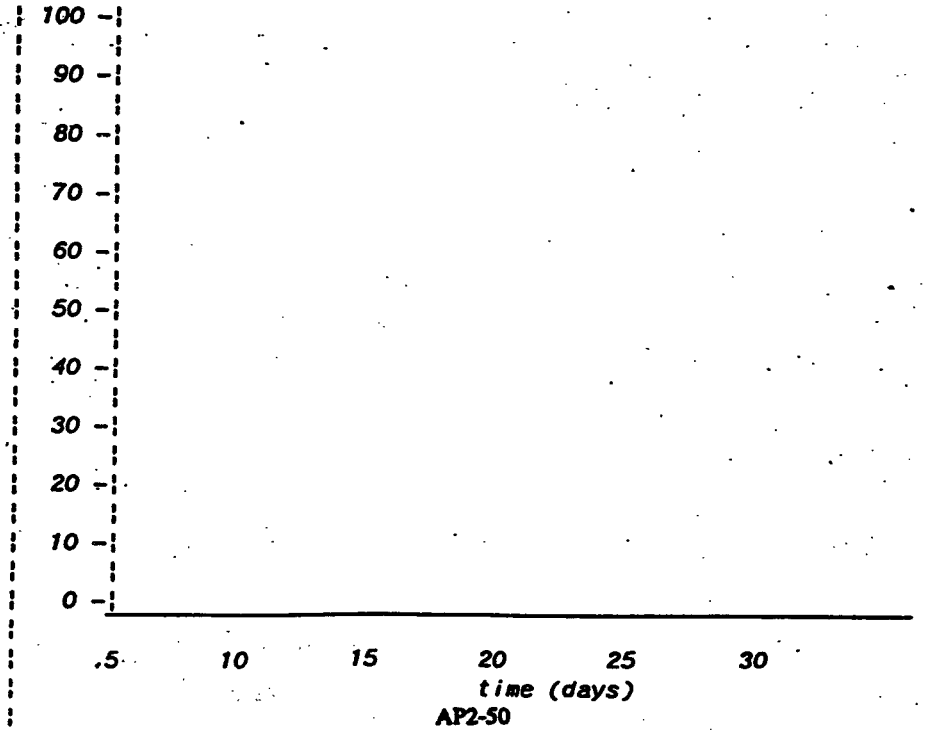
..... % degradation

Classification: readily biodegradable yes ☐ no ☐

Reference substance:

Experimental Values			
test substance		reference substance	
day	%	day	%

Degradation curve:



Method (type of test):

Body responsible for the test:

Comments:

5.2.1.2 BOD/COD

BOD (5 days) g/g	
COD g/g	
BOD/COD :	
Method (type of test):	
Body reponsible for the test:	
Comments:	

5.2.2 Hydrolysis as a function of pH

pH	T in °C	k-value in s^{-1}	$t_{1/2}$-value in h
4,0			
7,0			
9,0			

048

5.2.2 Hydrolysis as function of pH (continued)

Method:
Body responsible for the test:
Comments:

5.3 Any additional Ecotoxicological Tests, where available (for example: bioconcentration factor
adsorption/desorption
photodegradation)

Minimum information: End point investigated; Description of the essential features of the test method; Results; Test procedure used; Body responsible for the test; Comments.

6.1 For industry/skilled trades

6.1.1 Possibility of recovery/recycling of the used substance

6.1.2 Possibility of neutralization (of any potentially hazardous effects)

6.1.3 Possibility of destruction (where special techniques are necessary please indicate)

Controlled discharge:

Incineration:

Water purification system:

Others:

050

6.2 For the public at large

6.2.1 Possibility of recovery/recycling of the used substance

6.2.2 Possibility of neutralization (of any potentially hazardous effects)

6.2.3 Possibility of destruction

Controlled discharge:

Incineration:

Water purification system:

Others:

B DECLARATION CONCERNING THE UNFAVOURABLE EFFECTS ON MAN AND THE ENVIRONMENT FOR THE VARIOUS USES ENVISAGED

C PROPOSED CLASSIFICATION AND LABELLING OF THE SUBSTANCE IN ACCORDANCE WITH DIRECTIVE 79/831/EEC FOLLOWING THE CRITERIA OF ANNEX VI PART II B

Classification

- ☐ very toxic
- ☐ toxic
- ☐ harmful
- ☐ corrosive
- ☐ irritant
- ☐ explosive
- ☐ oxidising
- ☐ extremely flammable
- ☐ highly flammable
- ☐ flammable
- ☐ carcinogenic
- ☐ teratogenic
- ☐ mutagenic
- ☐ or otherwise dangerous to man or the environment
- ☐ not classified

Labelling

Symbol(s) and indication of danger(s) (in accordance with Annex II of Directive 67/548/EEC)

Risk phrases (in accordance with Annex III of Directive 67/548/EEC)

Safety phrases (in accordance with Annex IV of Directive 67/548/EEC)

053

D PROPOSALS FOR ANY RECOMMENDED PRECAUTIONS RELATING TO THE SAFE USE OF THE SUBSTANCE

ANNEX V

(This Annex replaces the title and Part II of Annex VI to Council Directive 67/548/EEC, as last amended by Directive 79/831/EEC)

ANNEX VI

General classification and labelling requirements for dangerous substances and preparations

PART I

Save where otherwise provided in the separate Directives on dangerous preparations, the substances and preparations shall be classified as very toxic, toxic or harmful according to the following criteria:

(a) Classification as very toxic, toxic or harmful shall be effected by determining the acute toxicity of the commercial substance or preparation in animals, expressed in LD_{50} or LC_{50} values with the following parameters being taken as reference values:

Category	LD_{50} absorbed orally in rat (mg/kg)	LD_{50} percutaneous absorption in rat or rabbit (mg/kg)	LC_{50} absorbed by inhalation in rat (mg/litre per 4 hours)
Very toxic	< 25	< 50	< 0,5
Toxic	25 – 200	50 – 400	0,5 – 2
Harmful	200 – 2 000	400 – 2 000	2 – 20

(b) If facts show that for the purposes of classification it is inadvisable to use the LD_{50} or LC_{50} values as a principal basis because the substances or preparations produce other effects, the substances or preparations shall be classified according to the magnitude of these effects.

PART II

Classification and labelling of dangerous substances and preparations; criteria for the choice of phrases indicating special risks (R-phrases) and safety advice (S-phrases)

CONTENTS

1. GENERAL INTRODUCTION

1.1. The object of classification is to identify all the toxicological, physico-chemical and ecotoxicological properties of substances and toxicological and physico-chemical properties of preparations which may constitute a risk during normal handling or use. Having identified any hazardous properties the substance or preparation must then be labelled to indicate the hazard(s) in order to protect the user, the general public and the environment.

1.2. This Annex sets out the general principles governing the classification and labelling of substances and preparations referred to in Article 3 (3) of Directive 67/548/EEC and in Article 3 (5) of Directive 88/379/EEC and other relevant Directives on dangerous preparations.

It is addressed to all those concerned (manufacturers, importers, national authorities) with methods of classifying and labelling dangerous substances and preparations.

1.3. The requirement of this Directive and of Directive 88/379/EEC are intended to provide a primary means by which the general public and persons at work are given essential information about dangerous substances and preparations. The label draws the attention of persons handling or using substances and preparations to the inherent danger of certain such materials.

The label may also serve to draw attention to more comprehensive product information on safety and use available in other forms.

1.4. The label takes account of all potential hazards which are likely to be faced in the normal handling and use of dangerous substances and preparations when in the form in which they are placed on the market, but not necessarily in any different form in which they may finally be used, e.g. diluted. The most severe hazards are highlighted by symbols, such hazards and those arising from other dangerous properties are specified in standard risk phrases, and safety phrases give advice on necessary precautions.

In the case of substances, the information is completed by the name of the substance under an internationally recognized chemical nomenclature, the preferred name being the one used in the European inventory of existing commercial chemical substances (Einecs), and the name and address of the person established in the Community who is responsible for placing the substance on the market.

In the case of preparations, the information is completed by the indication of the designation or the trade name of the preparation, the indication of the chemical name of the substances present in the preparation in accordance with Article 7 (1) (c) of Directive 88/379/EEC and the indication of the name, address and telephone number of the person established in the Community who is responsible for placing the preparation on the market.

1.5. With respect to substances referred to in the second subparagraph of Article 5 (2) of Directive 67/548/EEC, the labelling applied by the manufacturer or his representative remains valid until the substance is listed in Annex I or until a decision not to list it has been taken in accordance with the procedure laid down in Article 21.

1.6. For substances, the data required for classifiction and labelling may be obtained:

(a) as regards substances for which the information specified in Annex VII is required, most of the necessary data for classification and labelling appear in the 'base set'. This classification and labelling must be reviewed, if necessary, when further information is available (Annex VIII);

(b) as regards other substances (e.g. those referred to in Article 5 (2) of Directive 67/548/EEC), the data required for classification and labelling may if necessary be obtained from a number of different sources, for example the results of previous tests, information required by international rules on the transport of dangerous substances, information taken from reference works and the literature or information derived from practical experience.

For preparations, the data required for classification and labelling may be obtained:

(a) if it concerns physico-chemical data, by the application of the methods specified in Annex V to Directive 67/548/EEC. For gaseous preparations a calculation method may be used for flammable and oxidizing properties (see Chapter 9);

(b) — if it concerns data on health effects, by the application of the methods specified in Annex V to the Directive and/or by the application of the conventional method referred to in Article 3 (5) (a) to (i) of Directive 88/379/EEC,

— however if it concerns the evaluation of the carcinogenic, mutagenic and teratogenic properties, by the application of the conventional method referred to in Article 3 (5) (j) to (q) of Directive 88/379/EEC.

Note concerning the performance of animal tests

The performance of animal tests to establish experimental data is subject to the provisions of Directive 86/609/EEC regarding the protection of animals used for experimental purposes.

1.7. **Application of the guide criteria**

Several possibilities may occur according to whether it concerns substances or preparations. Classification must cover the toxicological and physico-chemical properties of substances and preparations and in addition, the ecotoxicological properties of substances. The object of choosing risk phrases is to ensure that the specific nature of the potential dangers identified in classification are expressed on the label. For this purpose it is necessary to consider the criteria given for the choice of symbol(s) and risk phrases in 2.2.1 to 2.2.6, 3.2.1 to 3.2.7 and Chapters 4 and 5 for substances only. For example, classification under 3.2.1 does not imply that the sections such as 3.2.2 or 3.2.4 can be ignored.

The criteria are applicable to gaseous substances and preparations but only in so far as they may be subject to the packaging and labelling provisions of this Directive or the separate Directive on preparations.

Notwithstanding the criteria given under 2.2.3, 2.2.4 and 2.2.5, substances and preparations in the form of aerosols shall be subject to the flammability criteria set out in 1.8 and 2.2 (c) of the Annex to Directive 75/324/EEC.

1.7.1. **Application of the guide criteria for substances**

The guidance criteria set out in this Annex are directly applicable when the data in question have been obtained from test methods comparable with those described in Annex V. In other cases, the available data must be evaluated by comparing the test methods employed with those indicated in Annex V and the rules specified in this Annex for determining the appropriate classification and labelling criteria.

Classification of substances containing impurities or additives which are classified as carcinogens

A substance containing an impurity or an additive which is classified as a carcinogen and labelled with R 45 must itself be classified as a carcinogen and labelled with R 45 if the concentration of the carcinogenic impurity or additive is equal to or exceeds:

— either the concentration of the impurity or the additive specified in Annex I, or

— the concentration of 0,1 % where the impurity or the additive appears in Annex I without a concentration limit. (However in the case of asbestos this general rule does not apply until a concentration limit has been fixed in Annex I. Substances which have asbestos impurities must be classified and labelled according to the principles in Article 5 (2)), or

— the concentration of 0,1 % where the impurity or the additive does not appear in Annex I.

NB: if a substance containing an impurity or additive which is classified as a carcinogen is used as part of a preparation, the preparation shall be classified as a carcinogen and labelled with R 45 only when the concentration of the carcinogenic impurity or additive equals or exceeds the limits shown above as a % weight of the impurity or additive in the preparation.

If the information regarding the carcinogenic impurity or additive on the label of the substance is insufficient to enable the manufacturer of a preparation to carry out the classification and labelling correctly, the person established within the Community responsible for placing the substance on the market, whether it be the manufacturer, the importer or the distributor, shall supply, upon justified request and if available, appropriate information about the impurity or additive responsible for the carcinogenic classification of the substance to enable the classification and labelling of the preparation.

1.7.2. **Application of the guide criteria for preparations**

The guidance criteria set out in this Annex are directly applicable when the data in question have been obtained from test methods comparable with those described in Annex V with the exception of the criteria of Chapter 4 for which only the conventional method is applicable. In other cases, the available data must be evaluated by comparing the test methods employed with those indicated in Annex V and the rules specified in this Annex for determining the appropriate classification and labelling criteria.

If the health hazards are assessed by applying the conventional method referred to in Article 3 (5) of Directive 88/379/EEC, the individual concentration limits to be used are those set out, either:

— in Annex I to Directive 67/548/EEC, or

— in Annex I to Directive 88/379/EEC where the substance or substances do not appear in Annex I to the Directive or appear in it without concentration limits.

In the case of preparations containing mixtures of gases, classification with respect to the health effects will be established by the calculation method on the basis of the individual concentration limits from Annex I to the Directive or, when these limits are not in Annex I, on the basis of the criteria of Annex I to Directive 88/379/EEC, as amended by Directive 90/462/EEC.

Preparations used as constituents of another preparation

The labelling of such preparations must be in conformity with the provisions of Article 7 according to the conditions foreseen in Article 3 of Directive 88/379/EEC. However, in certain cases, the information on the label of the preparation is insufficient to enable other manufacturers who wish to use it as a constituent of their own preparation(s) to carry out the classification and labelling of their preparation(s) correctly. In these cases, the person established within the Community responsible for placing the original preparation on the market, whether it be the manufacturer, the importer or the distributor, shall supply upon justified request and as soon as possible all necessary data concerning the dangerous substances present to enable correct classification and labelling of the new preparation. This data is also necessary to enable the person responsible for placing the new preparation on the market to comply with other requirements of Directive 88/379/EEC.

2. CLASSIFICATION ON THE BASIS OF PHYSICO-CHEMICAL PROPERTIES

2.1. Introduction

The test methods relating to explosive, oxidizing and flammable properties included in Annex V to this Directive serve to give specific meaning to the general definitions given in Article 2 (2) (a) to (e). Criteria follow directly from the test methods in Annex V as far as they are mentioned.

If adequate information is available to demonstrate in practice that the physico-chemical properties of substances and preparations (apart from organic peroxides) are different from those revealed by the test methods given in Annex V, then such substances and preparations should be classified according to the hazard they present, if any, to those handling the substances and preparations or to other persons.

2.2. Criteria for classification, choice of symbols, indication of danger and choice of risk phrases

In the case of preparations, the criteria referred to in Article 3 (2) of Directive 88/379/EEC need to be taken into consideration.

2.2.1. Explosive

Substances and preparations shall be classified as explosive and assigned the symbol 'E' and the indication of danger 'explosive' in accordance with the results of the tests given in Annex V and in so far as the substances and preparations are explosive as placed on the market. One risk phrase is obligatory, it is to be specified on the basis of the following:

R 2 Risk of explosion by shock, friction, fire or other sources of ignition

— Substances and preparations including certain organic peroxides but excepting those set out below.

R 3 Extreme risk of explosion by shock, friction, fire or other sources of ignition

— Substances and preparations which are particularly sensitive such as picric acid salts, PETN and certain undiluted organic peroxides such as dibenzoyl peroxide.

2.2.2. Oxidizing

Substances and preparations shall be classified as oxidizing and assigned the symbol 'O' and the indication of danger 'oxidizing' in accordance with the results of the tests given in Annex V. One risk phrase is obligatory, it is to be specified on the basis of the test results but subject to the following:

R 11 Highly flammable

— Organic peroxides which have flammable properties even when not in contact with other combustible material.

R 8 Contact with combustible material may cause fire

— Other oxidizing substances and preparations which may cause fire or enhance the risk of fire when in contact with combustible material.

R 9 Explosive when mixed with combustible material

— Other substances and preparations which become explosive when mixed with combustible materials, e.g. certain chlorates.

2.2.2.1. *Remarks concerning peroxides*

Organic peroxides are classified as dangerous on the basis of their structure (e.g. R-O-O-H; R_1-O-O-R_2). In general terms, organic peroxides shall be classified as oxidizing, and labelled as under 2.2.2, unless:

— tests carried out in accordance with the methods given in Annex V show the organic peroxide, in the form in which it is placed on the market, to have explosive properties, as under 2.2.1, or

— the organic peroxide is so diluted or phlegmatized to the point where it is no longer explosive, oxidizing or flammable.

2.2.3. Extremely flammable

Substances and preparations shall be classified as extremely flammable and assigned the symbol 'F+' and the indication of danger 'extremely flammable' in accordance with the results of the tests given in Annex V. The risk phrase shall be assigned in accordance with the following criteria:

R 12 Extremely flammable

— Liquid substances and preparations which have a flash point lower than 0 °C and a boiling point (or in case of a boiling range the initial boiling point) lower than or equal to 35 °C.

2.2.4. Highly flammable

Substances and preparations shall be classified as highly flammable and assigned the symbol 'F' and the indication of danger 'highly flammable' in accordance with the results of the tests given in Annex V. Risk phrases shall be assigned in accordance with the following criteria:

R 17 Spontaneously flammable in air

— Substances and preparations which may become hot and finally catch fire in contact with air at ambient temperature without any input of energy.

R 11 Highly flammable

— Solid substances and preparations which may readily catch fire after brief contact with a source of ignition and which continue to burn or to be consumed after removal of the source of ignition.

— Liquid substances and preparations having a flash point below 21 °C but which are not extremely flammable.

R 12 Extremely flammable

— Gaseous substances and preparations which are flammable in air at normal pressure.

R 13 Extremely flammable liquefied gas

— Gaseous substances and preparations which are flammable in air at normal pressure when put on the market in liquefied form.

R 15 Contact with water liberates highly flammable gases

— Substances and preparations which, in contact with water or damp air, evolve highly flammable gases in dangerous quantities, at a minimum rate of one litre per kilogram per hour.

2.2.5. Flammable

Substances and preparations shall be classified as flammable in accordance with the results of the tests given in Annex V. The risk phrase shall be assigned in accordance with the criteria mentioned below.

R 10 Flammable

— Liquid substances and preparations having a flash point equal to or greater than 21 °C, and less than or equal to 55 °C.

However, in practice it has been shown that a preparation having a flash point equal to or greater than 21 °C and less than or equal to 55 °C need not be classified as flammable if the preparation could not in any way support combustion and only so long as there is no reason to fear risks to those handling these preparations or to other persons.

2.2.6. Other physico-chemical properties

Additional risk phrases shall be assigned to substances and preparations which have been classified by virtue of 2.2.1 to 2.2.5 above or by Chapters 3, 4 and 5 below, in accordance with the following criteria (based on experience obtained during compilation of Annex I):

R 1 Explosive when dry

For explosive substances and preparations put on the market in solution or in a wetted form; e.g. nitrocellulose with more than 12,6 % nitrogen.

R 4 Forms very sensitive explosive metallic compounds

For substances and preparations which may form sensitive explosive metallic derivatives, e.g. picric acid, styphnic acid.

R 5 Heating may cause an explosion

For thermally unstable substances and preparations not classified as explosive, e.g. perchloric acid > 50 %.

R 6 Explosive with or without contact with air

For substances and preparations which are unstable at ambient temperatures, e.g. acetylene.

R 7 May cause fire

For reactive substances and preparations: e.g. fluorine, sodium hydrosulphite.

R 14 Reacts violently with water

For substances and preparations which react violently with water, e.g. acetyl chloride, alkali metals, titanium tetrachloride.

R 16 Explosive when mixed with oxidizing substances

For substances and preparations which react explosively with an oxidizing agent, e.g. red phosphorus.

R 18 In use, may form flammable/explosive vapour-air mixture

For preparations not in themselves classified as flammable, which contain volatile components which are flammable in air.

R 19 May form explosive peroxides

For substances and preparations which may form explosive peroxides during storage, e.g. diethyl ether, 1,4-dioxan.

R 30 Can become highly flammable in use

For preparations not in themselves classified as flammable, which may become flammable due to the loss of non-flammable volatile components.

R 44 Risk of explosion if heated under confinement

For substances and preparations not in themselves classified as explosive in accordance with 2.2.1 above but which may nevertheless display explosive properties in practice if heated under sufficient confinement. For example, certain substances which would decompose explosively if heated in a steel drum do not show this effect if heated in less-strong containers.

For other additional risk phrases see 3.2.7.

3. CLASSIFICATION ON THE BASIS OF TOXICOLOGICAL PROPERTIES

3.1. Introduction

3.1.1. Classification is concerned with both the acute and long-term effects of these substances and preparations, whether resulting from a single instance of exposure or repeated or prolonged exposure.

If adequate evidence is available to demonstrate in practice that the toxic effect of substances and preparations on man is, or is likely to be different from that suggested by the experimental results obtained in animal tests or by the application of the conventional method referred to in Article 3 (5) of Directive 88/379/EEC, then such substances and preparations should be classified according to their toxicity in man. However, tests on man should be discouraged and should not normally be used to negate positive animal data.

3.1.2. The classification of substances must be made on the basis of the experimental data available in accordance with the following criteria which take into account the magnitude of these effects:

(a) for acute toxicity (lethal and irreversible effects after a single exposure), the parameters indicated in Part I A of Annex VI and under 3.2.1 to 3.2.3 are to be used;

(b) for sub-acute, sub-chronic or chronic toxicity, the criteria under 3.2.2 to 3.2.4 are to be used;

(c) for corrosive and irritant effects, the criteria under 3.2.5 and 3.2.6 are to be used;

(d) for sensitizing effects, the criteria under 3.2.3 to 3.2.6 are to be used;

(e) for specific effects on health (carcinogenic, mutagenic and teratogenic effects), the criteria in Chapter 4 are to be used.

3.1.3. For preparations, the classification relating to dangerous for health is carried out:

(a) on the basis of the conventional method referred to in Article 3 (5) of Directive 88/379/EEC in the absence of experimental data. In this case, the classification is based on the individual concentration limits:

— either taken from Annex I to Directive 67/548/EEC,

— or from Annex I to Directive 88/379/EEC where the substance or substances do not appear in Annex I to Directive 67/548/EEC or appear in it without concentration limits;

(b) or when experimental data are available, according to the criteria described under 3.1.2. excluding the carcinogenic, mutagenic and teratogenic properties referred to under 3.1.2 (e) which must be evaluated by the conventional method referred to in Article 3 (5 (j) to (q) of Directive 88/379/EEC.

Whichever method is used for the evaluation of the danger of a preparation, all the dangerous effects on health as defined in Annex I to Directive 88/379/EEC must be taken into consideration.

3.1.4. When the classification is to be established from experimental results obtained in animal tests the results should have validity for man in that the tests reflect, in an appropriate way, the risks to man.

3.2. **Criteria for classification, choice of symbols, indication of danger, choice of risk phrases**

3.2.1. Very toxic

Substances and preparations shall be classified as very toxic and assigned the symbol 'T+' and the indication of danger 'very toxic' in accordance with the criteria given in Part I of Annex VI, as specified below.

Risk phrases shall be assigned in accordance with the following criteria:

R 28 Very toxic if swallowed

— Acute toxicity results

LD_{50} oral, rat: < 25 mg/kg

R 27 Very toxic in contact with skin

— Acute toxicity results

LD_{50} dermal, rat or rabbit: < 50 mg/kg

R 26 Very toxic by inhalation

— Acute toxicity results

LC_{50} inhalation, rat: < 0,5 mg/litre per 4 hours

R 39 (*) Danger of very serious irreversible effects

— Strong evidence that irreversible damage other than the effects referred to in Chapter 4 is likely to be caused by a single exposure by an appropriate route, generally in the abovementioned dose range (see also 3.1.2 and 3.1.3).

3.2.2. Toxic

Substances and preparations shall be classified as toxic and assigned the symbol 'T' and the indication of danger 'toxic' in accordance with the criteria given in Part I of Annex VI, as specified below. Risk phrases shall be assigned in accordance with the following criteria.

R 25 Toxic if swallowed

— Acute toxicity results

LD_{50} oral, rat: $25 < LD_{50} < 200$ mg/kg

R 24 Toxic in contact with skin

— Acute toxicity results

LD_{50} dermal, rat or rabbit: $50 < LD_{50} < 400$ mg/kg

R 23 Toxic by inhalation

— Acute toxicity results

LC_{50} inhalation, rat: $0,5 < LC_{50} < 2$ mg/litre per 4 hours

R 39 (*) Danger of very serious irreversible effects

— Strong evidence that irreversible damage other than the effects referred to in Chapter 4 is likely to be caused by a single exposure by an appropriate route, generally in the abovementioned dose range (see also 3.1.2 and 3.1.3).

R 48 (**) Danger of serious damage to health by prolonged exposure

— Serious damage (clear functional disturbance or morphological change which have toxicological significance) is likely to be caused by repeated or prolonged exposure by an appropriate route.

Substances are classified at least as toxic when these effects are observed at levels of one order of magnitude lower (i.e. ten-fold) than those set out for R 48 in 3.2.3.

(*) In order to indicate the route of administration/exposure the following combinations should be used: R 39/26, R 39/27, R 39/28, R 39/26/27, R 39/26/28, R 39/27/28, R 39/26/27/28.

(**) In order to indicate the route of administration/exposure one of the following combinations shall be used: R 39/23, R 39/24, R 39/25, R 39/23/24, R 39/23/25, R 39/24/25, R 39/23/24/25.

(**) In order to indicate route of administration/exposure one of the following combinations shall be used: R 48/23, R 48/24, R 48/25, R 48/23/24, R 48/23/25, R 48/24/25, R 48/23/24/25.

3.2.3. Harmful

Substances and preparations shall be classified as harmful and assigned the symbol 'Xn' and the indication of danger 'harmful' in accordance with the criteria given in Part I of Annex VI, as specified below. Risk phrases shall be assigned in accordance with the following criteria:

R 22 Harmful if swallowed

— Acute toxicity results

LD_{50} oral, rat: 200 < LD_{50} < 2 000 mg/kg

R 21 Harmful in contact with skin

— Acute toxicity results

LD_{50} dermal, rat or rabbit: 400 < LD_{50} < 2 000 mg/kg

R 20 Harmful by inhalation

— Acute toxicity results

LC_{50} inhalation, rat: 2 < LC_{50} < 20 mg/litre per 4 hours

R 40 (*) Possible risk of irreversible effects

— Strong evidence that irreversible damage other than the effects referred to in Chapter 4 is likely to be caused by a single exposure by an appropriate route, generally in the abovementioned dose range (see also 3.1.2 and 3.1.3).

R 42 May cause sensitization by inhalation

— If practical evidence is available which shows the substances and preparations to be capable of inducing a sensitization reaction in humans by inhalation, at a greater frequency than would be expected from the response of a general population.

R 48 (*) Danger of serious damage to health by prolonged exposure

— Serious damage (clear functional disturbance or morphological change which has toxicological significance) is likely to be caused by repeated or prolonged exposure by an appropriate route.

Substances are classified at least as harmful when these effects are observed at levels of the order of:

— oral, rat < 50 mg/kg (bodyweight) per day,

— dermal, rat or rabbit < 100 mg/kg (bodyweight) per day,

— inhalation, rat < 0,25 mg/litre per 6 hours per day.

These guide values can apply directly when severe lesions have been observed in a sub-chronic (90 days) toxicity test. When interpreting the results of a sub-acute (28 days) toxicity test these figures should be increased approximately three fold. If a chronic (two years) toxicity test is available it should be evaluated on a case-by-case basis. If results of studies of more than one duration are available, then those from the study of the longest duration should normally be used.

3.2.4. Comments regarding the use of R 48

Use of this risk phrase refers to the specific range of biological effects within the terms described below. It should be noted that the terms are not identical to the definitions of harmful and toxic in Article 2 (2) (g) and (h) of Directive 67/548/EEC. For application of this risk phrase serious damage to health is to be considered to include death, clear functional disturbance or morphological changes which are toxicologically significant. It is particularly important when these changes are irreversible. It is also important to consider not only specific severe changes in a single organ or biological system but also generalized changes of a less severe nature involving several organs, or severe changes in general health status.

When assessing whether there is evidence for these types of effects reference should be made to the following guidelines:

(*) In order to indicate route of administration/exposure one of the following combinations shall be used: R 40/20, R 40/21, R 40/22, R 40/20/21, R 40/20/22, R 40/21/22, R 40/20/21/22.

(*) In order to indicate route of administration/exposure one of the following combinations shall be used: R 48/20, R 48/21, R 48/22, R 48/20/21, R 48/20/22, R 48/21/22, R 48/20/21/22.

1. Evidence indicating that R 48 should be applied:

(a) Substance-related deaths

(b) (i) Major functional changes in the central or peripheral nervous systems, including sight, hearing and the sense of smell, assessed by clinical observations or other appropriate methods (e.g. electrophysiology).

(ii) Major functional changes in other organ systems (for example the lung).

(c) Any consistent changes in clinical biochemistry, haematology or urinalysis parameters which indicate severe organ dysfunction. Haematological disturbances are considered to be particularly important if the evidence suggests that they are due to decreased bone marrow production of blood cells.

(d) Severe organ damage noted on microscopic examination following autopsy.

(i) Widespread or severe necrosis, fibrosis or granuloma formation in vital organs with regenerative capacity (e.g. liver).

(ii) Severe morphological changes that are potentially reversible but are clear evidence of marked organ dysfunction (e.g. severe fatty change in the liver, severe acute tubular nephrosis in the kidney, ulcerative gastritis).

(iii) Evidence of appreciable cell death in vital organs incapable of regeneration (e.g. fibrosis of the myocardium or dying back of a nerve) or in stem cell populations (e.g. aplasia or hypoplasia of the bone marrow).

The above evidence will most usually be obtained from animal experiments. When considering data derived from practical experience special attention should be given to exposure levels.

2. Evidence indicating that R 48 should not be applied.

The use of this risk phrase is restricted to 'serious damage to health by prolonged exposure'. A number of substance-related effects may be observed in both humans and animals that would not justify the use of R 48. These effects are relevant when attempting to determine a no-effect level for a chemical substance. Examples of well documented changes which would not normally justify classification with R 48, irrespective of their statistical significance, include:

(a) clinical observations or changes in bodyweight gain, food consumption or water intake, which may have some toxicological importance but which do not, by themselves, indicate 'serious damage';

(b) small changes in clinical biochemistry, haematology or urinalysis parameters which are of doubtful or minimal toxicological importance;

(c) changes in organ weights with no evidence of organ dysfunction;

(d) adaptative responses (e.g. macrophage migration in the lung, liver hypertrophy and enzyme induction, hyperplastic responses to irritants). Local effects on the skin produced by repeated dermal application of a substance whihc are more appropriately classified with R 38 'irritating to skin';

(e) where a species-specific mechanism of toxicity (e.g. specific metabolic pathways) has been demonstrated.

3.2.5. Corrosive

A substance or a preparation is considered to be corrosive if, when it is applied to healthy intact animal skin, it produces full thickness destruction of skin tissue on at least one animal during the test for skin irritation cited in Annex V or during an equivalent method or if the results can be predicted, for example from strongly acid or alkaline reactions. Classification can be based on the results of validated *in vitro* tests.

The substance or preparation shall be classified as corrosive and assigned the symbol 'C' and the indication of danger 'corrosive'. Risk phrases shall be assigned in accordance with the following criteria:

R 35 Causes severe burns

— If, when applied to healthy intact animal skin, full thickness destruction of skin tissue occurs as a result of up to three minutes exposure, or if this result can be predicted.

R 34 Causes burns

— If, when applied to healthy intact animal skin, full thickness destruction of skin tissue occurs as a result of up to four hours exposure, or if this result can be predicted.

3.2.6. Irritant

Non-corrosive substances and preparations shall be classified as irritant and assigned the symbol 'Xi' and the indication of danger 'irritant' in accordance with the criteria given below.

1. Inflammation of the skin

Inflammation of the skin which persists for at least 24 hours after an exposure period of up to four hours and corresponds to the following values determined on the rabbit according to the cutaneous irritation test method cited in Annex V:

— the mean value of the scores for either erythema and eschar formation or oedema formation, calculated over all the animals tested, is two or more,

— or, in the case where the Annex V test has been completed using three animals, either erythema and eschar formation or oedema formation equivalent to a mean value of two or more calculated for each animal separately has been observed in two or more animals.

In both cases all scores at each of the reading times (24, 48 and 72 hours) for an effect should be used in calculating the respective mean values.

The following risk phrase shall be assigned in accordance with the criteria given:

R 38 Irritating to skin

— If, when applied to healthy intact animal skin for up to four hours, significant inflammation is caused and which persists for 24 hours or more after the end of the exposure period.

Inflammation is significant if the mean value of the scores is two or more for either erythema and eschar formation or oedema formation. The same shall be the case where the test has been completed using three animals if the score for either erythema and eschar formation or oedema formation observed in two or more animals is equivalent to the value of two or more.

2. Ocular lesion

Ocular lesions which occur within 72 hours after exposure and which persist for at least 24 hours and correspond to the following values determined on the rabbit according to the eye irritation test method cited in Annex V:

— the mean value of the scores for each type of lesion, calculated over all the animals tested, is one of the following:

  — cornea opacitytwo or more,

  — iris lesion one or more,

  — redness of conjunctivae 2,5 or more,

  — oedema of conjunctivae (chemosis) two or more, or

— in the case where the Annex V test has been completed using three animals, either cornea opacity, iris lesion, redness of conjunctivae or oedema of conjunctivae (chemosis) equivalent to a mean value such as is quoted above, but calculated for each animal separately, has been observed in two or more animals.

In both cases all scores at each of the reading times (24, 48, 72 hours) and for an effect should be used in calculating the respective mean values.

The following risk phrases shall also be assigned in accordance with the criteria given:

R 36 Irritating to eyes

— If, when applied to the eye of the animal, significant ocular lesions are caused and which persist for 24 hours or more after instillation of the test material.

Ocular lesions are significant if the means of the scores have any of the values: Cornea opacity equal to or greater than 2 but less than 3; iris lesion equal to or greater than 1 but not greater than 1,5; redness of the conjunctivae equal to or greater than 2,5; oedema of the conjunctivae (chemosis) equal to or greater than 2. The same shall be the case where the test has been completed using three animals if the lesions, on two or more animals, are equivalent to any of the above values except that for iris lesion the value should be equal to or greater than 1 but less than 2 and for redness of conjunctivae the value should be equal to or greater than 2,5.

R 41 (*) Risk of serious damage to eyes

— If when applied to the eye of the animal severe ocular lesions are caused and which are present 24 hours or more after instillation of the test material.

Ocular lesions are severe if the means of the scores have any of the values:

Cornea opacity equal to or greater than 3; iris lesion greater than 1.5. The same shall be the case where the test has been completed using three animals if these lesions, on two or more animals, have any of the values:

Cornea opacity equal to or greater than 3; iris lesion equal to 2.

R 43 May cause sensitization by skin contact

— If practical experience shows the substances and preparations to be capable of inducing a sensitization reaction in a substantial number of persons by skin contact, or on the basis of a positive response in experimental animals.

In the case of the adjuvent type test method for skin sensitization detailed in Annex V or in the case of other adjuvant-type test methods, a response of at least 30 % of the animals is considered positive. For any other test method a response of at least 15 % of the animals is considered positive.

R 37 Irritating to respiratory system

— Substances and preparations which cause serious irritation to the respiratory system, based normally on practical observation.

3.2.7. Other toxicological properties

Additional risk phrases shall be assigned to substances and preparations classified by virtue of 2.2.1 to 3.2.6 above and/or Chapters 4 and 5, in accordance with the following criteria (based on experience obtained during compilation of Annex I):

R 29 Contact with water liberates toxic gas

For substances and preparations which in contact with water or damp air, evolve very toxic/toxic gases in potentially dangerous amounts, e.g. aluminium phosphide, phosphorus pentasulphide.

R 31 Contact with acids liberates toxic gas

For substances and preparations which react with acids to evolve toxic gases in dangerous amounts, e.g. sodium hypochlorite, barium polysulphide. For substances used by members of the general public, the use of S 50 (do not mix with .....(to be specified by the manufacturer)) would be more suitable.

R 32 Contact with acids liberates very toxic gas

For substances and preparations which react with acids to evolve very toxic gases in dangerous amounts; e.g. salts of hydrogen cyanide, sodium azide. For substances used by members of the general public, the use of S 50 (do not mix with .....(to be specified by the manufacturer)) would be more suitable.

R 33 Danger of cumulative effects

For substances and preparations when accumulation in the human body is likely and may cause some concern which, however, is not sufficient to justify the use of R 48.

Previously assigned to substances of Annex I and preparations which were likely to cause damage to health by prolonged exposure or which were likely to be retained and then accumulated within the human body. Now to be progressively replaced when appropriate by R 48.

When substances labelled with R 33 are present in preparations, R 33 shall be included in the label at all concentrations where a label is required by the Directive on dangerous preparations.

For other risk phrases see 2.2.6.

(*) The of R 34 or R 35 precludes the use of R 41.

4. CLASSIFICATION ON THE BASIS OF SPECIFIC EFFECTS ON HUMAN HEALTH

4.1. Introduction

4.1.1. This chapter sets out the procedure for the classification of substances which may have the effects mentioned below.

4.1.2. If a manufacturer or his representative has information available which indicates that a substance should be classified and labelled in accordance with the criteria given in 4.2.1, 4.2.2 or 4.2.3, he or his representative shall provisionally label the substance in accordance with these criteria, unless the conclusions reached by the application of the criteria mentioned in 3.2.1 to 3.2.5 indicate the need for a more severe classification.

4.1.3. The manufacturer or his representative shall submit as soon as possible a document summarizing all relevant information to one Member State in which the substance is placed on the market. This summary document should include a bibliography containing all relevant references, including any relevant unpublished data.

4.1.4. Furthermore, a manufacturer or his representative who has new data which are relevant to the classification and labelling of a substance in accordance with the criteria given in 4.2.1, 4.2.2 or 4.2.3, shall submit this data as soon as possible to one Member State in which the substance is placed on the market.

4.1.5. In order to obtain as quickly as possible a harmonized classification for the Community by the procedure defined in Article 21 of Directive 67/548/EEC, Member States which have relevant information available justifying the classification of a substance in one of these categories, whether submitted by the manufacturer or not, should forward such information together with suggestions for classification and labelling, to the Commission as soon as possible.

The Commission will forward to the other Member States the classification and labelling proposal that it receives. Any Member State may ask the Commission for the information it has received.

Any Member State which has good reason to believe that the suggested classification and labelling is inappropriate as far as the carcinogenic, mutagenic or teratogenic effects are concerned shall notify the Commission thereof.

4.1.6. The provisional labelling applied by a manufacturer or his representative shall remain valid until the entry into force of a decision on the inclusion or non-inclusion of the substance concerned in Annex I.

4.2. Criteria for classification, indication of danger, choice of risk phrases

4.2.1. Carcinogenic substances

For the purpose of classification and labelling, and having regard to the current state of knowledge, such substances are divided into three categories:

Category 1

Substances known to be carcinogenic to man. There is sufficient evidence to establish a causal association between human exposure to a substance and the development of cancer.

Category 2

Substances which should be regarded as if they are carcinogenic to man. There is sufficient evidence to provide a strong presumption that human exposure to a substance may result in the development of cancer, generally on the basis of:

— appropriate long-term animal studies,

— other relevant information.

Category 3

Substances which cause concern for man owing to possible carcinogenic effects but in respect of which the available information is not adequate for making a satisfactory assessment. There is some evidence from appropriate animal studies, but this is insufficient to place the substance in category 2.

4.2.1.1. The following symbols and specific risk phrases apply:

Categories 1 and 2:

T; R 45 may cause cancer

However for substances and preparations which present a carcinogenic risk only when inhaled, for example, as dust, vapour or fumes, (other routes of exposure e.g. by swallowing or in contact with skin do not present any carcinogenic risk), the following symbol and specific risk phrase should be used:

T; R 49 may cause cancer by inhalation

Category 3:

Xn; R 40 possible risk of irreversible effects

4.2.1.2. Comments regarding the categorization of carcinogenic substances

The placing of a substance into category 1 is done on the basis of epidemiological data; placing into categories 2 and 3 is based primarily on animal experiments.

For classification as a category 2 carcinogen either positive results in two animal species should be available or clear positive evidence in one species, together with supporting evidence such as genotoxicity data, metabolic or biochemical studies, induction of benign tumours, structural relationship with other known carcinogens, or data from epidemiological studies suggesting an association.

Category 3 actually comprises 2 sub-categories:

(a) substances which are well investigated but for which the evidence of a tumour-inducing effects is insufficient for classification in category 2. Additional experiments would not be expected to yield further relevant information with respect to classification,

(b) substances which are insufficiently investigated. The available data are inadequate, but they raise concern for man. This classification is provisional; further experiments are necessary before a final decision can be made.

For a distinction between categories 2 and 3 the arguments listed below are relevant which reduce the significance of experimental tumour induction in view of possible human exposure. These arguments, especially in combination, would lead in most cases to classification in category 3, even though tumours have been induced in animals:

— carcinogenic effects only at very high dose levels exceeding the 'maximal tolerated dose'. The maximal tolerated dose is characterized by toxic effects which, although not yet reducing lifespan, go along with physical changes such as about 10 % retardation in weight gain,

— appearance of tumours, especially at high dose levels, only in particular organs of certain species known to be susceptible to a high spontaneous tumour formation,

— appearance of tumours, only at the site of application, in very sensitive test systems (e.g., i.p. or s.c. application of certain locally active compounds), if the particular target is not relevant to man,

— lack of genotoxicity in short-term tests *in vivo* and *in vitro*,

— existence of a secondary mechanism of action with the implication of a practical threshold above a certain dose level (e.g. hormonal effets on target organs or on mechanisms of physiological regulation, chronic stimulation of cell proliferation),

— existence of a species-specific mechanism of tumour formation (e.g. by specific metabolic pathways) irrelevant for man.

For a distinction between category 3 and no classification arguments are relevant which exclude a concern for man:

— a substance should not be classified in any of the categories if the mechanism of experimental tumour formation is clearly identified, with good evidence that this process cannot be extrapolated to man,

— if the only available tumour data are liver tumours in certain sensitive strains of mice, without any other supplementary evidence, the substance may not be classified in any of the categories,

— particular attention should be paid to cases where the only available tumour data are the occurrence of neoplasms at sites and in strains where they are well known to occur spontaneously with a high incidence.

4.2.2. Mutagenic substances

4.2.2.1. For the purposes of classification and labelling, and having regard to the current state of knowledge, such substances are divided into three categories:

Category 1:

Substances known to be mutagenic to man.

There is sufficient evidence to establish a causal association between human exposure to a substance and heritable genetic damage.

Category 2:

Substances which should be regarded as if they are mutagenic to man.

There is sufficient evidence to provide a strong presumption that human exposure to the substance may result in the development of heritable genetic damage, generally on the basis of:

— appropriate animal studies,

— other relevant information.

Category 3:

Substances which cause concern for man owing to possible mutagenic effects. There is evidence from appropriate mutagenicity studies, but this is insufficient to place the substance in category 2.

4.2.2.2. The following symbols and specific risk phrases apply:

Category 1:

T; R 46 may cause heritable genetic damage

Category 2:

Xn; R 46 may cause heritable genetic damage

Category 3:

Xn; R 40 possible risk of irreversible effects

4.2.2.3. Comments regarding the categorization of mutagenic substances

Definition of terms:

A mutation is a permanent change in the amount or structure of the genetic material in an organism, resulting in a change of the phenotypic characteristics of the organism. The alterations may involve a single gene, a block of genes, or a whole chromosome. Effects involving single genes may be a consequence of effects on single DNA bases (point mutations) or of large changes, including deletions, within the gene. Effects on whole chromosomes may involve structural or numerical changes. A mutation in the germ cells in sexually reproducing organisms may be transmitted to the offspring. A mutagen is an agent that gives rise to an enhanced occurrence of mutations.

It should be noted that substances are classified as mutagens with specific reference to inherited genetic damage. However, the type of results leading to classification of chemicals in category 3: 'induction of genetically relevant events in somatic cells', is generally also regarded as an alert for possible carcinogenic activity.

Method development for mutagenicity testing is an ongoing process. For many new tests no standardized protocols and evaluation criteria are presently available. For the evaluation of mutagenicity data the quality of the test performance and the degree of validation of the test method have to be considered.

Category 1:

To place a substance in category 1, positive evidence from human mutation epidemiology studies will be needed. Examples of such substances are not known to date. It is recognized that it is extremely difficult to obtain reliable information from studies on the incidence of mutations in human populations, or on possible increases in their frequencies.

Category 2:

To place a substance in category 2, positive results are needed from assays showing (a) mutagenic effects, or (b) other cellular interactions relevant to mutagenicity, in germ cells of mammals *in vivo*, or (c) mutagenic effects in somatic cells of mammals *in vivo* in combination with clear evidence that the substance or a relevant metabolite reaches the germ cells.

With respect to placement in category 2, at present the following methods are appropriate:

2 (a) *In vivo* germ cell mutagenicity assays:
- — specific locus mutation test,
- — heritable translocation test,
- — dominant lethal mutation test.

These assays actually demonstrate the appearance of affected progeny or a defect in the developing embryo.

2 (b) *In vivo* assays showing relevant interaction with germ cells (usually DNA):
- — assays for chromosomal abnormalities, as detected by cytogenetic analysis, including aneuploidy, caused by malsegregation of chromosomes,
- — test for sister chromatid exchanges (SCE's),
- — test for unscheduled DNA synthesis (UDS),
- — assay of (covalent) binding of mutagen to germ cell DNA,
- — assaying other kinds of DNA damage.

These assays provide evidence of a more or less indirect nature. Positive results in these assays would normally be supported by positive results from *in vivo* somatic cell mutagenicity assays, in mammals or in man (see under category 3, preferably methods as under 3 (a)).

2 (c) *In vivo* assays showing mutagenic effects in somatic cells of mammals (see under 3 (a)), in combination with toxicokinetic methods, or other methodologies capable of demonstrating that the compound or a relevant metabolite reaches the germ cells.

For 2 (b) and 2 (c), positive results from host-mediated assays or the demonstration of unequivocal effects in *in vitro* assays can be considered as supporting evidence.

Category 3

To place a substance in category 3, positive results are needed in assays showing (a) mutagenic effects or (b) other cellular interaction relevant to mutagenicity, in somatic cells in mammals *in vivo*. The latter especially would normally be supported by positive results from *in vitro* mutagenicity assays.

For effects in somatic cells *in vivo* at present the following methods are appropriate:

3 (a) *In vivo* somatic cell mutagenicity assays:
- — bone marrow micronucleus test or metaphase analysis,
- — metaphase analysis of peripheral lymphocytes,
- — mouse coat colour spot test.

3 (b) *In vivo* somatic cell DNA interaction assays:
- — test for SCE's in somatic cells,
- — test for UDS in somatic cells,
- — assay for the (covalent) binding of mutagen to somatic cell DNA,
- — assay for DNA damage, e.g. by alkaline elution, in somatic cells.

Substances showing positive results only in one or more *in vitro* mutagenicity assays should normally not be classified. Their further investigation using *in vivo* assays, however, is strongly indicated. In exceptional cases, e.g. for a substance showing pronounced responses in several *in vitro* assays, for which no relevant *in vivo* data are available, and which shows resemblance to known mutagens/carcinogens, classification in category 3 could be considered.

4.2.3. **Teratogenic substances**

4.2.3.1. For the purpose of classification and labelling, and having regard to the current state of knowledge, such substances are divided into two categories:

Category 1

Substances known to be teratogenic to man.

There is sufficient evidence to establish a causal association between human exposure to a substance and subsequent non-heritable birth defects in offspring.

Category 2

Substances which should be regarded as if they are teratogenic to man.

There is sufficient evidence to provide a strong presumption that human exposure to the substance may result in non-heritable birth defects in offspring, generally on the basis of:

— appropriate animal studies,

— other relevant information.

4.2.3.2. The following symbols and specific risk phrases apply:

Category 1

T; R 47 may cause birth defects

Category 2

Xn; R 47 may cause birth defects

4.2.4. **Procedure for the classification of preparations concerning specific effects on health**

If a preparation contains one or more substances classified with respect to the criteria laid out above, it must be classified according to the criteria referred to in Article 3 (5) (j) to (q) of Directive 88/379/EEC (the limits of concentration are either in Annex I to this Directive, or in Annex I to Directive 88/379/EEC where the substance or substances under consideration do not appear in Annex I or appear in it without concentration limits).

5. **CLASSIFICATION ON THE BASIS OF ENVIRONMENTAL EFFECTS**

5.1. **Introduction**

The primary objective of classifying substances dangerous for the environment is to alert the user to the hazards these substances present to ecosystems. Although the present criteria refer to aquatic ecosystems it is recognized that certain substances may simultaneously or alternatively affect other ecosystems whose constituents may range from soil microflora and microfauna to primates.

The criteria set out below follow directly from the test methods set out in Annex V, in so far as they are mentioned. The test methods required for the 'base set' referred to in Annex VII are limited and the information derived from them may be insufficient for an appropriate classification. Classification may require additional data derived from level 1 (Annex VIII) or other equivalent studies. Furthermore, classified substances may be subject to review in the light of other new data.

For the purposes of classification and labelling and having regard to the current state of knowledge such substances are divided into two groups according to their acute and/or long-term effects in aquatic systems or their acute and/or long-term effects in non-aquatic systems. In addition those substances classified according to the criteria set out under 5.2.1.1. and 5.2.2 will be assigned the symbol 'N' and the appropriate indication of danger after the pertinent amendment to Directive 67/548/EEC enters into force.

5.2. **Criteria for classification, indication of danger, choice of risk phrases**

5.2.1. **Aquatic environment**

5.2.1.1. Substances shall be classified as dangerous for the environment (*) and assigned risk phrases in accordance with the following criteria:

R 50 Very toxic to aquatic organisms
and
R 53 May cause long-term adverse effects in the aquatic environment

Acute toxicity:	96 hr LC_{50} (for fish)	< 1 mg/litre
or	48 hr EC_{50} (for Daphnia)	< 1 mg/litre
or	72 hr IC_{50} (**) (for algae)	< 1 mg/litre
and	the substance is not readily degradable (***)	
or	the log Pow (log octanol/water partition coefficient) > 3,0 (unless the experimentally determined BCF < 100)	

R 50 Very toxic to aquatic organisms

Acute toxicity:	96 hr LC_{50} (for fish)	< 1 mg/litre
or	48 hr EC_{50} (for Daphnia)	< 1 mg/litre
or	72 hr IC_{50} (**) (for algae)	< 1 mg/litre

R 51 Toxic to aquatic organisms
and
R 53 May cause long-term adverse effects in the aquatic environment

acute toxicity:	96 hr LC_{50} (for fish)	1 mg/litre	< LC_{50}	< 10 mg/litre
or	48 hr EC_{50} (for Daphnia)	1 mg/litre	< EC_{50}	< 10 mg/litre
or	72 hr IC_{50} (**) (for algae)	1 mg/litre	< IC_{50}	< 10 mg/litre
and	the substance is not readily degradable (***)			
or	the log Pow > 3.0 (unless the experimentally determined BCF < 100)			

5.2.1.2. Substances shall be classified as dangerous for the environment in accordance with the criteria set out below. Risk phrases shall also be assigned in accordance with the following criteria

R 52 Harmful to aquatic organisms
and
R 53 May cause long-term adverse effects in the aquatic environment

acute toxicity:	96 hr LC_{50} (for fish):	10 mg/litre	< LC_{50}	< 100 mg/litre
or	48 hr EC_{50} (for Daphnia):	10 mg/litre	< EC_{50}	< 100 mg/litre
or	72 hr IC_{50} (**) (for algae):	10 mg/litre	< IC_{50}	< 100 mg/litre
and	the substance is not readily degradable (***). This criterion applies unless there exists additional scientific evidence concerning degradation and/or toxicity sufficient to provide an adequate assurance that neither the substance nor its degradation products will constitute a potential long-term and/or delayed danger to the aquatic environment.			

(*) After the pertinent amendment to Directive 67/548/EEC enters into force, the symbol 'N' and the appropriate indication of danger will be assigned to these substances.

(**) Where it can be demonstrated in the case of highly coloured substances that algal growth is inhibited solely as a result of a reduction in light intensity, then the 72 h IC_{50} for algae should not be used as a basis for classification.

(***) Substances are considered readily degradable if the following criteria hold true:

(A) If in 28-day biodegradation studies the following levels of degradation are achieved:
— in tests based upon dissolved organic carbon: 70 %,
— in tests based upon oxygen depletion or carbon dioxide generation: 60 % of the theoretical maxima.
These levels of biodegradation must be achieved within 10 days of the start of degradation, which point is taken as the time when 10 % of the substance has been degraded.

OR

(B) If in those cases where only COD and BOD_5 data are available when the ration BOD_5/COD is greater than or equal to 0,5.

OR

(C) If other convincing scientific evidence is available to demonstrate that the substance can be degraded (biotically and/or abiotically) in the aquatic environment to a level of > 70 % within a 28-day period.

Such additional scientific evidence should normally be based on the studies required at level 1 (Annex VIII), or studies of equivalent value, and could include:

(i) a proven potential to degrade rapidly in the aquatic environment;

(ii) an absence of chronic toxicity effects at a concentration of 1,0 mg/litre, e.g. a no-observed effect concentration or greater than 1,0 mg/litre determined in a prolonged toxicity study with fish or Daphnia.

At least one of the following phrases:

R 52 Harmful to aquatic organisms

R 53 May cause long-term adverse effects in the aquatic environment

Substances not falling under the criteria listed above in this chapter, but which on the basis of the available evidence concerning their toxicity, persistence, potential to accumulate and predicted, or observed, environmental fate and behaviour may nevertheless present a danger immediate or long-term and/or delayed, to the structure and/or functioning of aquatic ecosystems. Poorly water soluble substances i.e. substances with a solubility of less than 1 mg/litre will be covered by this criteria if:

(a) they are not readily degradable (*); and

(b) the log Pow > 3,0 (unless the experimentally determined BCF < 100).

This criterion applies unless there exists additional evidence concerning degradation and/or toxicity sufficient to provide an adequate assurance that neither the substance nor its degradation products will constitute a potential long-term and/or delayed danger to the aquatic environment.

Such additional scientific evidence should normally be based on the studies required at level 1 (Annex VIII), or studies of equivalent value, and could include:

(i) a proven potential to degrade rapidly in the aquatic environment;

(ii) an absence of chronic toxicity effects at the solubility limit, e.g. a no-observed effect concentration of greater than a solubility limit determined in a prolonged toxicity study with fish or Daphnia.

5.2.2. Non-aquatic environment

Substances shall be classified as dangerous for the environment (**) in accordance with the criteria set out below.

At least one of the following phrases shall be assigned in accordance with the following criteria:

R 54 Toxic to flora
R 55 Toxic to fauna
R 56 Toxic to soil organisms
R 57 Toxic to bees
R 58 May cause long-term adverse effects in the environment
R 59 Dangerous for the ozone layer

} (***)

Substances which on the basis of the available evidence concerning their toxicity, persistence, potential to accumulate and predicted or observed environmental fate and behaviour may present a danger, immediate or long-term and/or delayed, to the structure and/or functioning of natural ecosystems other than those covered under 5.2.1 above.

(*) Substances are considered readily degradable if the following criteria hold true:

(A) If in 28-day biodegradation studies the following levels of degradation are achieved:

— in tests based upon dissolved organic carbon: 70 %,

— in tests based upon oxygen depletion or carbon dioxide generation: 60 % of the theoretical maxima.

These levels of biodegradation must be achieved within 10 days of the start of degradation, which point is taken as the time when 10 % of the substance has been degraded.

OR

(B) If in those cases where only COD and BOD, data are available when the ration BOD_5/COD is greater than or equal to 0,5.

OR

(C) If other convincing scientific evidence is available to demonstrate that the substance can be degraded (biotically and/or abiotically) in the aquatic environment to a level of > 70 % within a 28-day period.

(**) After the pertinent amendment to Directive 67/548/EEC enters into force, the symbol 'N' and the appropriate indication of danger will be assigned to these substances.

(***) Detailed criteria, along with other risk phrases will be elaborated later.

6. CHOICE OF SAFETY ADVICE PHRASES

6.1. Safety phrases for substances and preparations

Safety advice phrases (S-phrases) shall be assigned to substances and preparations in accordance with the following general criteria. In addition, for certain preparations, safety advice is listed in Annex II to Directive 88/379/EEC. Whenever the manufacturer is mentioned in Chapter 6 it refers to the person responsible for placing the substance or preparation on the market.

S 1 *Keep locked up*

— Applicability:

— Very toxic and toxic substances and preparations.

— Criteria for use:

— Recommended for very toxic and toxic substances and preparations likely to be used by members of the general public.

S 2 *Keep out of reach of children*

— Applicability:

— All dangerous substances and preparations.

— Criteria for use:

— Obligatory only for all dangerous substances and preparations likely to be used by members of the general public or likely to be used in places to which the general public have access unless there is no reason to fear any danger particularly to children.

S 3 *Keep in a cool place*

— Applicability:

— Organic peroxides.

— Other dangerous substances and preparations having a boiling point < 40 °C.

— Criteria for use:

— Obligatory for organic peroxides unless S 47 is used.

— Recommended for other dangerous substances and preparations having a boiling point < 40 °C.

S 4 *Keep away from living quarters*

— Applicability:

— Very toxic and toxic substances and preparations.

— Criteria for use:

— Normally limited to very toxic and toxic substances and preparations when desirable to supplement S 13; for example when there is an inhalation risk and the substance or preparation should be stored away from living quarters. The advice is not intended to preclude proper use of the substance or preparation in living quarters.

S 5 *Keep contents under...* (appropriate liquid to be specified by the manufacturer)

— Applicability:

— Spontaneously flammable solid substances and preparations.

— Criteria for use:

— Normally limited to special cases, e.g. sodium, potassium or white phosphorous.

S 6 *Keep under...* (inert gas to be specified by the manufacturer)

— Applicability:

— Dangerous substances and preparations which must be kept under an inert atmosphere.

— Criteria for use:

— Normally limited to special cases, e.g. certain organo-metallic compounds.

S 7 *Keep container tightly closed*

— Applicability:

— Organic peroxides.

— Substances and preparations which can give off very toxic, toxic, harmful, extremely flammable or highly flammable vapours.

— Substances and preparations which in contact with moisture give off highly flammable gases.

— Highly flammable solids.

— Criteria for use:

— Obligatory for organic peroxides in the combination of S 3/7/9.

— Recommended for the other fields of application mentioned above.

S 8 *Keep container dry*

— Applicability:

— Substances and preparations which may react violently with water.

— Substances and preparations which on contact with water liberate highly flammable gases.

— Substances and preparations which on contact with water liberate very toxic or toxic gases.

— Criteria for use:

— Normally limited to the fields of application mentioned above when necessary to reinforce warnings given by R 14, R 15 in particular, and R 29.

S 9 *Keep container in a well-ventilated place*

— Applicability:

— Organic peroxides.

— Volatile substances and preparations which may give off very toxic, toxic or harmful vapours.

— Extremely flammable or highly flammable liquids and gases.

— Criteria for use:

— Obligatory for organic peroxides in the combination S 3/7/9.

— Recommended for volatile substances and preparations which may give off very toxic, toxic or harmful vapours.

— Recommended for extremely flammable or highly flammable liquids or gases.

S 12 *Do not keep the container sealed*

— Applicability:

— Substances and preparations which will by giving off gases or vapours be liable to burst the container.

— Criteria for use:

— Normally limited to the special cases mentioned above.

S 13 *Keep away from food, drink and animal feedingstuffs*

— Applicability:

— Very toxic, toxic and harmful substances and preparations.

— Criteria for use:

— Recommended when such substances and preparations are likely to be used by members of the general public.

S 14 *Keep away from...* (incompatible materials to be indicated by the manufacturer)

— Applicability:

— Organic peroxides.

— Criteria for use:

— Obligatory for and normally limited to organic peroxides. However, may be useful in exceptional cases when incompatibility is likely to produce a particular risk.

S 15 *Keep away from heat*

— Applicability:

— Substances and preparations which may decompose or which may react spontaneously under the effect of heat.

— Criteria for use:

— Normally limited to special cases, e.g. monomers, but not assigned if risk phrases R 2, R 3 and/or R 5 have already been applied.

S 16 *Keep away from sources of ignition — no smoking*

— Applicability:

— Extremely flammable or highly flammable liquids and gases.

— Criteria for use:

— Recommended for the substances and preparations mentioned above but not assigned if risk phrases R 2, R 3 and/or R 5 have already been applied.

S 17 *Keep away from combustible material*

— Applicability:

— Substances and preparations which may form explosive or spontaneously flammable mixtures with combustible material.

— Criteria for use:

— Available for use in special cases, e.g. to emphasize R 8 and R 9.

S 18 *Handle and open container with care*

— Applicability:

— Substances and preparations liable to produce an overpressure in the container.

— Substances and preparations which may form explosive peroxides.

— Criteria for use:

— Normally limited to the abovementioned cases when there is risk of damage to the eyes and/or when the substances and preparations are likely to be used by members of the general public.

S 20 *When using do not eat or drink*

— Applicability:

— Very toxic, toxic and corrosive substances and preparations.

— Criteria for use:

— Normally limited to special cases (e.g. arsenic and arsenic compounds; fluoracetates) in particular when any of these are likely to be used by members of the general public.

S 21 *When using do not smoke*

— Applicability:

— Substances and preparations which produce toxic products on combustion.

— Criteria for use:

— Normally limited to special cases (e.g. halogenated compounds).

S 22 *Do not breathe dust*

— Applicability:

— All solid dangerous substances and preparations.

— Criteria for use:

— Recommended for those substances and preparations mentioned above which are liable to form inhalable dusts, and when it is necessary to draw the attention of the user to inhalation risks not mentioned in the risk phrases which have been ascribed. However, may be used in exceptional cases to emphasize such risk phrases, in particular to emphasize R 42.

S 23 *Do not breathe gas/fumes/vapour/spray* (appropriate wording to be specified by the manufacturer)

— Applicability:

— All liquid or gaseous dangerous substances and preparations.

— Criteria for use:

— Recommended when it is necessary to draw the attention of the user to inhalation risks not mentioned in the risk phrases which have to be ascribed. However, may be used in exceptional cases to emphasize such risk phrases, in particular to emphasize R 42.

— Recommended for substances and preparations in the form of aerosols which are likely to be used by members of the general public.

S 24 *Avoid contact with skin*

— Applicability:

— All dangerous substances and preparations.

— Criteria for use:

— Recommended when it is necessary to draw the attention of the user to skin contact risks not mentioned in the risk phrases which have to be ascribed. However, may be used to emphasize such risk phrases, in particular to emphasize R 43.

S 25 *Avoid contact with eyes*

— Applicability:

— Corrosive or irritant substances and preparations.

— Criteria for use:

— Normally limited to special cases, i.e. when it is considered essential to emphasize the risk to eyes denoted by use of R 34, R 35, R 36 or R 41. Thus important if these substances and preparations are likely to be used by members of the general public and eye or face protection may not be available.

S 26 *In case of contact with eyes, rinse immediately with plenty of water and seek medical advice*

— Applicability:

— Corrosive or irritant substances and preparations.

— Criteria for use:

— Obligatory for corrosive substances and preparations and those to which R 41 has already been ascribed.

— Recommended for irritant substances to which the risk phrase R 36 has already been ascribed.

S 27 *Take off immediately all contaminated clothing*

— Applicability:

— Organic peroxides.

— Very toxic, toxic or corrosive substances and preparations.

— Criteria for use:

— Obligatory for organic peroxides.

— Recommended for very toxic and toxic substances and preparations which are easily absorbed by the skin and for corrosive substances and preparations unless safety phrase S 36 can be considered sufficient by itself.

S 28 *After contact with skin, wash immediately with plenty of...* (to be specified by the manufacturer)

— Applicability:

— Very toxic, toxic or corrosive substances and preparations.

— Criteria for use:

— Recommended for the substances and preparations mentioned above, in particular when water is not the most appropriate rinsing fluid.

S 29 *Do not empty into drains*

— Applicability:

— Extremely or highly flammable liquids.

— Criteria for use:

— Recommended for those extremely or highly flammable liquids which are immiscible with water. The intention is to avoid accidents (e.g. fire explosion) and not to emphasize general pollution problems.

S 30 *Never add water to this product*

— Applicability:

— Substances and preparations which react violently with water.

— Criteria for use:

— Normally limited to special cases (e.g. sulphuric acid) and may be used, as appropriate, to give the clearest possible information, either to emphasize R 14 or as an alternative to R 14.

S 33 *Take precautionary measures against static discharges*

— Applicability:

— Extremely or highly flammable substances and preparations.

— Criteria for use:

— Recommended for substances and preparations used in industry which do not absorb moisture. Virtually never used for substances and preparations as placed on the market for use by members of the general public.

S 34 *Avoid shock and friction*

— Applicability:

— Explosive substances and preparations.

— Criteria for use:

— Obligatory for and normally limited to explosive organic peroxides.

S 35 *This material and its container must be disposed of in a safe way*

— Applicability:

— Explosive substances and preparations.

— Very toxic and toxic substances and preparations.

— Criteria for use:

— Obligatory for explosive substances and preparations other than organic peroxides.

— Recommended for very toxic and toxic substances and preparations, particularly when such substances and preparations are likely to be used by members of the general public.

S 36 *Wear suitable protective clothing*

— Applicability:

— Very toxic, toxic or harmful substances and preparations.

— Corrosive substances and preparations.

— Criteria for use:

— Recommended for substances and preparations used in industry which are:

— very toxic, toxic or corrosive, and/or

— harmful and easily absorbed by the skin, and/or

— liable to damage health by prolonged exposure.

S 37 *Wear suitable gloves*

— Applicability:

— Very toxic, toxic, harmful or corrosive substances and preparations.

— Organic peroxides.

— Substances and preparations irritating to the skin.

— Criteria for use:

— Recommended for very toxic, toxic and corrosive substances and preparations when S 36 is not used (e.g. viz general public).

— Recommended for organic peroxides as combination S 37/39.

— Recommended for substances and preparations irritating to the skin particularly when R 38 is not shown on the label.

S 38 *In case of insufficient ventilation wear suitable respiratory equipment*

— Applicability:

— Very toxic or toxic substances and preparations.

— Criteria for use:

— Normally limited to special cases involving the use of very toxic or toxic substances and preparations in industry or in agriculture.

S 39 *Wear eye/face protection*

— Applicability:

— Organic peroxides.

— Corrosive substances and preparations, including irritants which give rise to risk of serious damage to the eyes.

— Very toxic and toxic substances and preparations

— Criteria for use:

— Recommended for organic peroxides as the combination S 37/39.

— Recommended for the corrosive substances and preparations mentioned above, in particular when there is a risk of splashing.

— Normally limited to exceptional cases for very toxic and toxic substances and preparations, where there is a risk of splashing and they are likely to be easily absorbed by the skin.

S 40 *To clean the floor and all objects contaminated by this material use...* (to be specified by the manufacturer)

— Applicability:

— All dangerous substances and preparations.

— Criteria for use:

— Normally limited to those dangerous substances and preparations for which water is not considered to be a suitable cleansing agent (e.g. where absorption by powdered material, dissolution by solvent etc. is necessary) and where it is important for health and/or safety reasons to provide a warning on the label.

S 41 *In case of fire and/or explosion do not breathe fumes*

— Applicability:

— Dangerous substances and preparations which on combustion give off very toxic or toxic gases.

— Criteria for use:

— Normally limited to special cases.

S 42 *During fumigation/spraying wear suitable respiratory equipment* (appropriate wording to be specified by the manufacturer)

— Applicability:

— Substances and preparations intended for such use but which may endanger the health and safety of the user unless proper precautions are taken.

— Criteria for use:

— Normally limited to special cases.

S 43 *In case of fire use...* (indicate in the space the precise type of fire-fighting equipment. If water increases the risk add: Never use water)

— Applicability:

— Extremely flammable, highly flammable and flammable substances and preparations.

— Criteria for use:

— Obligatory for substances and preparations which in contact with water or damp air, evolve highly flammable gases.

— Recommended for extremely flammable, highly flammable and flammable substances and preparations, particularly when they are immiscible with water.

S 44 *If you feel unwell seek medical advice* (show the label where possible)

— Applicability:

— Toxic substances and preparations.

— Criteria for use:

— Obligatory for the substances and preparations mentioned above when used in industry and not likely to be used by members of the general public.

S 45 *In case of accident or if you feel unwell seek medical advice immediately* (show the label where possible)

— Applicability:

— Very toxic substances and preparations.

— Toxic substances and preparations.

— Criteria for use:

— Obligatory for the very toxic substances and preparations mentioned above.

— Obligatory for toxic substances and preparations mentioned above when likely to be used by members of the general public.

S 46 *If swallowed, seek medical advice immediately and show this container or label*

— Applicability:

— All dangerous substances and preparations other than those which are toxic or very toxic.

— Criteria for use:

— Obligatory for all dangerous substances and preparations mentioned above which are likely to be used by members of the general public, unless there is no reason to fear any danger from swallowing, particularly by children.

S 47 *Keep at temperature not exceeding ... °C* (to be specified by the manufacturer)

— Applicability:

— Substances and preparations which become unstable at a certain temperature.

— Criteria for use:

— Normally limited to special cases (e.g. certain organic peroxides).

S 48 *Keep wetted with ...* (appropriate material to be specified by the manufacturer)

— Applicability:

— Substances and preparations which may become very sensitive to sparks, friction or impact if allowed to dry out.

— Criteria for use:

— Normally limited to special cases, e.g. nitrocelluloses.

S 49 *Keep only in the original container*

— Applicability:

— Substances and preparations sensitive to catalytic decomposition.

— Criteria for use:

— Substances and preparations sensitive to catalytic decomposition e.g. certain organic peroxides.

S 50 *Do not mix with ...* (to be specified by the manufacturer)

— Applicability:

— Substances and preparations which may react with the specified product to evolve very toxic or toxic gases.

— Organic peroxides.

— Criteria for use:

— Recommended for substances and preparations mentioned above which are likely to be used by members of the general public, when it is a better alternative to R 31 or R 32.

— Obligatory with certain peroxides which may give violent reaction with accelerators or promoters.

S 51 *Use only in wellventilated areas*

— Applicability:

— Substances and preparations likely to or intended to produce vapours, dusts, sprays, fumes, mists, etc. which give rise to inhalation risks or to a fire or explosion risk.

— Criteria for use:

— Recommended when use of S 38 would not be appropriate. Thus important when such substances and preparations are likely to be used by members of the general public.

S 52 *Not recommended for interior use on large surface areas*

— Applicability:

— Volatile, very toxic, toxic and harmful substances and preparations containing them.

— Criteria for use:

— Recommended when damage to health is likely to be caused by prolonged exposure to these substances by reason of their volatilization from large treated surfaces in the home or other enclosed places where persons congregate.

S 53 *Avoid exposure — obtain special instructions before use*

— Applicability:

— Carcinogenic, mutagenic and/or teratogenic substances and preparations.

— Criteria for use:

— Obligatory for the abovementioned substances and preparations to which at least one of the following R—phrases have been assigned: R 45, R 46, R 47 or R 49.

6.2. **Safety phrases assigned to substances dangerous for the environment**

The complexity of the environment and the variety of uses to which chemical substances are put are such that it is not possible to specify precisely the most appropriate safety phrases. Those assigning safety phrases should consider such supplementary information as may be provided with the substances and select phrases from the following:

S 54 *Obtain the consent of pollution control authorities before discharging to wastewater treatment plants*

— Applicability and criteria for use:

— Applies to substances which may affect the functioning of sewage treatment plant processes and sludge disposal.

— Recommended for substances which are very toxic, toxic or harmful to aquatic organisms or which may cause long-term adverse effects in the aquatic environment.

— Recommended when such substances are used in industry.

S 55 *Treat using the best available techniques before discharge into drains or the aquatic environment.*

— Applicability and criteria for use:

— Recommended for substances which are very toxic, toxic or harmful to aquatic organisms or substances which may cause long-term adverse effects for which treatment techniques are available.

— Recommended when such substances are used in industry.

S 56 *Do not discharge into drains or the environment, dispose to an authorised waste collection point*

— Applicability and criteria for use:

— Recommended for substances which are very toxic or toxic to aquatic organisms or which may cause long-term adverse effects in the aquatic environment.

S 57 *Use appropriate containment to avoid environmental contamination*

— Applicability and criteria for use:

— Recommended for substances which are very toxic or toxic to aquatic organisms and particularly for substances which may cause long-term adverse effects in the aquatic or non-aquatic environment.

— Substances toxic to flora, fauna, soil or other organisms.

— Recommended when such substances are used in industry.

S 58 *To be disposed of as hazardous waste*

— Applicability and criteria for use:

— Recommended for substances which are very toxic, toxic or harmful to aquatic organisms or substances which may cause long-term adverse effects in the non-aquatic or aquatic environment.

— Recommended for substances toxic to flora, fauna, bees or other organisms.

S 59 *Refer to manufacturer/supplier for information on recovery/recycling*

— Applicability and criteria for use:

— Obligatory for substances dangerous for the ozone layer.

— Recommended for substances which are toxic to flora, fauna, soil organisms, bees or substances which may cause long-term adverse effects in the environment.

S 60 *This material and/or its container must be disposed of as hazardous waste*

— Applicability and criteria for use:

— This phrase should be used in place of S 58 in cases where contaminated containers require disposal.

— Recommended for substances which are very toxic, toxic or harmful to aquatic organisms or substances which may cause long—term adverse effects in the non—aquatic or aquatic environment.

— Recommended for substances toxic to flora, fauna, bees or other organisms.

7. LABELLING

7.1. When a substance or preparation has been classified the appropriate label is determined with reference to the requirements of Article 16 of Directive 67/548/EEC (79/831/EEC) and Article 7 of Directive 88/379/EEC for substances and preparations respectively. This section explains how the label is determined and, in particular, gives guidance on how to choose the appropriate risk and safety phrases.

The label of a substance or a preparation should be derived from the total number of symbols, risk phrases and safety phrases assigned. It is based on:

(a) the determination of the categories of danger and indications of danger;

(b) the determination and final choice of the phrases indicating particular risks (R-phrases);

(c) the determination and final choice of the phrases indicating safety advice (S-phrases);

(d) the final choice of the name or names which will appear on the label.

7.2. Choice of R-phrases

7.2.1. For substances, R-phrases will be selected according to the following criteria and priorities:

(a) in the case of health effects:

(i) R-phrases corresponding to the category of danger illustrated by a symbol — these phrases must appear on the label;

(ii) R-phrases corresponding to other categories of danger which are not illustrated by a symbol by virtue of Article 16 (4) of Directive 67/548/EEC;

(b) in the case of danger arising from physico-chemical properties:

— the criteria described under 7.2.1 (a) above are applicable, except that the risk phrases 'extremely flammable' or 'highly flammable' need not be indicated where they repeat the wording of the indication of danger used with a symbol;

(c) in the case of danger for the environment:

— the R-phrases corresponding to the classification category dangerous for the environment — these phrases must appear on the label.

7.2.2. For preparations, R-phrases will be selected according to the following criteria and priorities:

(a) in the case of dangers which give rise to health effects:

(i) R-phrases which correspond to the category of danger illustrated by a symbol. In certain cases the R-phrases must be adapted according to the tables of Annex I to Directive 88/379/EEC. More specifically, the R-phrases of the constituent(s) which are responsible for the assignment of the preparation to a danger category must appear on the label;

(ii) R-phrases which correspond to the other categories of danger which have been attributed to the constituents but which are not illustrated by a symbol by virtue of Article 7 (d) of Directive 88/379/EEC;

(b) in the case of dangers arising from physico-chemical properties:

— the criteria described under 7.2.2 (a) are applicable, except that the risk phrases 'extremely flammable' or 'highly flammable' need not be indicated where they repeat the wording of the indication of danger used with a symbol.

7.3. Final choice of risk and safety phrases

Although the final choice of the most appropriate risk and safety phrases is primarily governed by the need to give all necessary information, consideration should also be given to the clarity and impact of the label. With clarity in mind, the necessary information should be expressed in a minimum number of phrases.

7.3.1. Risk phrases

As a general rule, applying to substances and preparations, a maximum of four R-phrases shall suffice to describe the risk; for this purpose the combined phrases listed in Annex III shall be regarded as single phrases. However, the standard phrases must cover all the principal hazards associated with the preparation.

However, where there is a need to identify environmental hazards additional R-phrases shall be added as required.

7.3.2. Safety phrases

The final choice of safety phrases must have regard to the risk phrases indicated on the label and to the intended use of the substance or preparation:

— safety phrases which give obvious advice in relation to risk phrases are generally omitted from the label unless used to give particular emphasis to a specific warning,

— certain safety phrases, e.g. S 2, have particular relevance to substances and preparations intended to be used by the public, other phrases have particular relevance to persons at work. Phrases should be chosen with the intended use in view,

— particular attention must be given, in the choice of safety phrases, to the foreseen conditions of use of certain substances and preparations, e.g. spraying or other aerosol effects,

— as a general rule, a maximum of four S-phrases shall suffice to formulate the most appropriate safety advice; for this purpose the combined phrases listed in Annex IV shall be regarded as single phrases,

— in the case of danger to the environment a minimum of one and a maximum of four S-phrases should be used,

— some R-phrases become superfluous if a careful selection is made of S-phrases and vice-versa. S-phrases which obviously correspond to R-phrases will appear on the label only if it is intended to emphasize a specific warning.

7.4. Chemical name(s) to be displayed on the label:

(a) for substances:

the name is established according to an internationally recognized chemical nomenclature as defined in 1.4.

(b) for preparations:

the choice of the names to be displayed on the label follows the rules of Article 7 (1) (c) of Directive 88/379/EEC.

Note

In the case of concentrate preparations which are intended for the perfume industry:

— the person responsible for placing them on the market may identify merely the one sensitizing substance judged by him to be primarily responsible for the sensitization hazard;

— in the case of a natural substance, the chemical name may be of the type: 'essential oil of ...', 'extract of ...', rather than the name of the constituents of that essential oil.

7.5. Note

It is important to remember that Annex II of Directive 88/379/EEC has special provisions concerning the labelling of certain preparations.

8. SPECIAL CASES: SUBSTANCES

8.1. *Metals in massive form*

These substances are classified in Annex I to Directive 67/548/EEC or shall be classified in accordance with Article 5 (2) of Directive 67/548/EEC. However, some of these substances although classified in accordance with Article 2 of Directive 67/548/EEC do not present a danger to human health by inhalation, ingestion or contact with skin in the form in which they are placed on the market. Such substances do not require a label according to Article 16 of this Directive. However, all the information which should have appeared on the label shall be transmitted to the user by the person responsible for placing the metal on the market.

9. SPECIAL CASES: PREPARATIONS

9.1. Gaseous preparations (gas mixtures)

For gaseous preparations, consideration must be given to:

— the evaluation of the physico-chemical properties,

— the evaluation of health hazards.

9.1.1. Evaluation of physico-chemical properties

9.1.1.1. *Flammability*

The flammable properties of these preparations are determined in accordance with Article 3 (2) of Directive 88/379/EEC according to the methods specified in Part A of Annex V to Directive 67/548/EEC. These preparations will be classified according to the results of the tests carried out and with respect to the criteria of Annex V and to the criteria of the labelling guide. However, by derogation, in the case where gaseous preparations are produced to order in small amounts, the flammability of these gaseous mixtures can be evaluated by the following calculation method:

The expression of the gaseous mixture

$$A_1F_1 + \ldots + A_iF_i + \ldots A_nF_n + B_1I_1 + \ldots B_jI_j + \ldots B_pI_p$$

where: A_i and B_j are the molar fractions
F_i flammable gas
I_j inert gas
n number of inert gases
p number of inert gases

can be transformed in a form where all the I_j (inert gases) are expressed by a nitrogen equivalent using a coefficient K_j and where the equivalent content of inflammable gas A'_i is expressed as follows:

$$A'_i = A_i \times \left(\frac{100}{(A_i + K_jB_j)}\right)$$

By using the value of the maximum content of flammable gas which, in a mixture with nitrogen, gives a composition which is not flammable in air (Tci), the following expression can be obtained:

$$\sum_i A'_i/Tci < 1$$

The gas mixture is flammable if the value of the above expression is greater than one and the preparation is classified highly flammable; furthermore, the phrase R 12 or R 13 will be assigned according to the case.

Coefficients of equivalency (Ki)

The values of the coefficients of equivalency Ki, between the inert gases and nitrogen and the values of the maximum contents of flammable gas (Tci) may be found in Tables 1 and 2 of the ISO Standard ISO/DIS 10156.

Maximum content of flammable gas (Tci)

The value of the maximum content of flammable gas (Tci) may be found in Table 2 of the ISO Standard ISO/DIS 10156. When a Tci value for a flammable gas does not appear in the above standard, the corresponding lower explosivity limit (LEL) will be used. If no LEL value exists, the value of Tci will be set at 1 % by volume.

Remarks

— The expression above can be used to allow an appropriate labelling of gaseous preparations, however, it should not be regarded as a method for replacing experimentation for the determination of technical safety parameters.

— Furthermore, this expression gives no information as to whether a mixture containing oxidizing gases can be prepared safely. When estimating flammability these oxidizing gases are not taken into account.

— The expression above will give reliable results only if the flammable gases do not influence each other as far as their flammability is concerned. This has to be considered, e.g. with halogenated hydrocarbons.

9.1.1.2. *Oxidizing properties*

Given the fact that Annex V to Directive 67/548/EEC does not contain a method to determine the oxidizing properties of gaseous mixtures, the evaluation of these properties must be realized according to the following estimation method.

The principle of the method is comparison of the oxidizing potential of gases in a mixture with that of the oxidizing potential of oxygen in air. The concentrations of gases in the mixture are expressed in % vol.

It is considered that the gas mixture is as oxidant as or more oxidant than air, if the following condition is verified:

$$\sum_i x_i C_i > 21$$

where: x_i is the concentration of gas i in % vol
C_i is the coefficient of oxygen equivalency

In this case, the preparation is classified as oxidizing and the phrase R 8 will be assigned.

Coefficients of equivalency between oxidizing gases and oxygen

The coefficients used in the calculation to determine the oxidizing capacity of certain gases in a mixture with respect to the oxidizing capacity of oxygen in air, listed under 5.2 in the ISO Standard ISO/DIS 10156, are the following.

O_2	1
N_2O	0,6

When no value for the C_i coefficient exists for a gas in the cited standard a value of 40 is attributed to this coefficient.

9.1.2. Evaluation of the health effects

This evaluation of the dangers of a preparation for health is made according to Article 3 (3).

When the evaluation of the health hazards is made according to the conventional method described in Article 3 (5) of Directive 88/379/EEC by reference to individual concentration limits, the individual concentration limits to be used are expressed in per cent by volume and appear:

— either in Annex I to Directive 67/548/EEC for the gas(es) considered,

— or in Annex I to Directive 88/379/EEC, Tables I A to VI A, when the gas(es) considered are not in Annex I, or appear there without concentration limits.

9.1.3. Labelling

For mobile gas holders the requirements concerning labelling are considered to be satisfied when they are in agreement with Article 8 (5) (b).

However, by way of derogation from Article 8 (1) and (2), for gas cylinders with a water capacity of less than or equal to 150 litres, the format and dimensions of the label can follow the prescriptions of the ISO Standard ISO/DP 7225. In this case, the label can bear the generic name or industrial/commercial name of the preparation provided that the dangerous component substances of the preparation are shown on the body of the gas cylinder in a clear and indelible way.

9.2. Alloys, preparations containing polymers, preparations containing elastomers

These preparations shall be classified according to the requirements of Article 3 and labelled according to the requirements of Article 7 of Directive 88/379/EEC.

However some of these preparations although classified in accordance with Article 3 (3) do not present a danger to human health by inhalation, ingestion or contact with skin in the form in which they are placed on the market. Such preparations do not require a label according to Article 7; however all the information which would have appeared on the label shall be transmitted to the professional user by means of an information system in a format foreseen in Article 10 of the abovementioned Directive.

COMMISSION STATEMENT

With regard to 4.1.5, and in particular to the last paragraph of 4.1.5, the Commission states that, should it envisage making use of the procedure of Article 21 of Directive 67/548/EEC, it is prepared to consult in advance appropriate experts designated by Members States and having special qualifications with respect to either carcinogenicity, mutagenicity or teratogenicity.

This consultation will take place in the framework of the normal consultation procedure with national experts and/or in the framework of existing committees. The same will be the case when substances already included in Annex I must be reclassified in respect of their carcinogenic, mutagenic or teratogenic effects.

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tion of records must be submitted. The reporting period will be specified by the letter or notice but in no case will such reporting period be less than 45 days from the date of the letter or the effective date of the notice.

(c) *How to report.* When required to report, firms must submit copies of records (preferably by certified mail) to: Document Processing Center (TS-790) Rm. L-100, Office of Toxic Substances, Environmental Protection Agency, 401 M St., SW., Washington, DC 20460. ATTN: 8(c) Allegations.

(Approved by the Office of Management and Budget under control number 2070-0017)

[48 FR 38187, Aug. 22, 1983, as amended at 49 FR 23183, June 5, 1984; 52 FR 20084, May 29, 1987; 53 FR 12523, Apr. 15, 1988]

§ 717.19 Confidentiality.

(a) Any person submitting copies of records may assert a business confidentiality claim covering all or part of the submitted information. Any information covered by a claim will be disclosed by EPA only as provided in procedures set forth at Part 2 of this title.

(b) If no claim accompanies a document at the time it is submitted to EPA, the document will be placed in an open file available to the public without further notice to the respondent.

(c) To asset a claim of confidentiality for information contained in a submitted record, the respondent must submit two copies of the document.

(1) One copy must be complete. In that copy, the respondent must indicate what information, if any, is claimed as confidential by marking the specific information on each page with a label such as "confidential", "proprietary", or "trade secret" and briefly state the basis of the claim.

(2) If some information is claimed as confidential, the respondent must submit a second copy of the record. The second copy must be complete, except that all information claimed as confidential in the first copy must be deleted.

(3) The first copy will be for internal use by EPA. The second copy will be placed in an open file to be available [illegible] public.

(4) Failure to furnish a second copy when information is claimed as confidential in the first copy will be considered a presumptive waiver of the claim of confidentiality. EPA will notify the respondent by certified mail that a finding of a presumptive waiver of the claim of confidentiality has been made. The respondent will be given 30 days from the date of receipt of notification to submit the required second copy. If the respondent fails to submit the second copy within the 30 days, EPA will place the first copy in the public file.

PART 720—PREMANUFACTURE NOTIFICATION

Subpart A—General Provisions

Subpart B—Applicability

Subpart C—Notice Form

Subpart D—Disposition of Notices

Subpart E—Confidentiality and Public Access to Information

AUTHORITY: 15 U.S.C. 2604, 2607, and 2613.

SOURCE: 48 FR 21742, May 13, 1983, unless otherwise noted.

Subpart A—General Provisions

§ 720.1 Scope.

This part establishes procedures for the reporting of new chemical substances by manufacturers and importers under section 5 of the Toxic Substances Control Act, 15 U.S.C. 2604. The rule defines the persons and chemical substances subject to the reporting requirements, prescribes the contents of section 5 notices, and establishes procedures for submitting notices. The rule also establishes EPA policy regarding claims of confidentiality for, and public disclosure of, various categories of information submitted in connection with section 5 notices.

(Approved by the Office of Management and Budget under control number 2070-0012)

§ 720.3 Definitions.

(a)(1) For the purposes of this part, the terms "cosmetic," "device," "drug," "food," and "food additive" have the meanings contained in the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 321 *et seq.*, and the regulations issued under it. In addition, the term "food" includes poultry and poultry products, as defined in the Poultry Products Inspection Act, 21 U.S.C. 453 *et seq.*; meats and meat food products, as defined in the Federal Meat Inspection Act, 21 U.S.C. 60 *et seq.*; and eggs and egg products, as defined in the Egg Products Inspection Act, 21 U.S.C. 1033 *et seq.*

(2) The term "pesticide" has the meaning contained in the Federal Insecticide, Fungicide, and Rodenticide Act, 7 U.S.C. 136 *et seq.* and the regulations issued under it.

(3) The terms "byproduct material," "source material," and "special nuclear material" have the meanings contained in the Atomic Energy Act of 1954, 42 U.S.C 2014 *et seq.* and the regulations issued under it.

(b) "Act" means the Toxic Substances Control Act, 15 U.S.C. 2601 *et seq.*

(c) "Article" means a manufactured item (1) which is formed to a specific shape or design during manufacture, (2) which has end use function(s) dependent in whole or in part upon its shape or design during end use, and (3) which has either no change of chemical composition during its end use or only those changes of composition which have no commercial purpose separate from that of the article and that may occur as described in § 720.36(g)(5), except that fluids and particles are not considered articles regardless of shape or design.

(d) "Byproduct" means a chemical substance produced without a separate commercial intent during the manufacture, processing, use, or disposal of another chemical substance or mixture.

(e) "Chemical substance" means any organic or inorganic substance of a particular molecular identity, including any combination of such substances occurring in whole or in part as a result of a chemical reaction or occurring in nature, and any chemical element or uncombined radical, except that "chemical substance" does not include:

(1) Any mixture.

(2) Any pesticide when manufactured, processed, or distributed in commerce for use as a pesticide.

(3) Tobacco or any tobacco product.

(4) Any source material, special nuclear material, or byproduct material.

(5) Any pistol, firearm, revolver, shells, or cartridges.

(6) Any food, food additive, drug, cosmetic, or device, when manufac-

tured, processed, or distributed in commerce for use as a food, food additive, drug, cosmetic, or device.

(f) "Commerce" means trade, traffic, transportation, or other commerce (1) between a place in a State and any place outside of such State, or (2) which affects trade, traffic, transportation, or commerce between a place in a State and any place outside of such State.

(g) "Customs territory of the United States" means the 50 States, Puerto Rico, and the District of Columbia.

(h) "Director" means the Director of the EPA Office of Toxic Substances.

(i) "Distribute in commerce" means to sell in commerce, to introduce or deliver for introduction into commerce, or to hold after introduction into commerce.

(j) "EPA" means the U.S. Environmental Protection Agency.

(k) "Health and safety study" or "study" means any study of any effect of a chemical substance or mixture on health or the environment or on both, including underlying data and epidemiological studies, studies of occupational exposure to a chemical substance or mixture, toxicological, clinical, and ecological, or other studies of a chemical substance or mixture, and any test performed under the Act. Chemical identity is always part of a health and safety study.

(1) Not only is information which arises as a result of a formal, disciplined study included, but other information relating to the effects of a chemical substance or mixture on health or the environment is also included. Any data that bear on the effects of a chemical substance on health or the environment would be included.

(2) Examples include:

(i) Long- and short-term tests of mutagenicity, carcinogenicity, or teratogenicity; data on behavioral disorders; dermatoxicity; pharmacological effects; mammalian absorption, distribution, metabolism, and excretion; cumulative, additive, and synergistic effects; acute, subchronic, and chronic effects; and structure/activity analyses.

(ii) Tests for ecological or other environmental effects on invertebrates, fish, or other animals, and plants, including: Acute toxicity tests, chronic toxicity tests, critical life stage tests, behavioral tests, algal growth tests, seed germination tests, plant growth or damage tests, microbial function tests, bioconcentration or bioaccumulation tests, and model ecosystem (microcosm) studies.

(iii) Assessments of human and environmental exposure, including workplace exposure, and impacts of a particular chemical substance or mixture on the environment, including surveys, tests, and studies of: Biological, photochemical, and chemical degradation; air, water, and soil transport; biomagnification and bioconcentration; and chemical and physical properties, e.g., boiling point, vapor pressure, evaporation rates from soil and water, octanol/water partition coefficient, and water solubility.

(iv) Monitoring data, when they have been aggregated and analyzed to measure the exposure of humans or the environment to a chemical substance or mixture.

(v) Any assessments of risk to health and the environment resulting from the manufacture, processing, distribution in commerce, use, or disposal of the chemical substance.

(l) "Importer" means any person who imports a chemical substance, including a chemical substance as part of a mixture or article, into the customs territory of the United States. "Importer" includes the person primarily liable for the payment of any duties on the merchandise or an authorized agent acting on his or her behalf. The term also includes, as appropriate:

(1) The consignee.

(2) The importer of record.

(3) The actual owner if an actual owner's declaration and superseding bond has been filed in accordance with 19 CFR 141.20; or

(4) The transferee, if the right to draw merchandise in a bonded warehouse has been transferred in accordance with Subpart C of 19 CFR Part 144. (See "principal importer.")

(m) "Impurity" means a chemical substance which is unintentionally present with another chemical substance.

(n) "Intermediate" means any chemical substance that is consumed, in whole or in part, in chemical reactions used for the intentional manufacture of another chemical substance(s) or mixture(s), or that is intentionally present for the purpose of altering the rates of such chemical reactions.

(o) "Inventory" means the list of chemical substances manufactured or processed in the United States that EPA compiled and keeps current under section 8(b) of the Act.

(p) "Known to or reasonably ascertainable by" means all information in a person's possession or control, plus all information that a reasonable person similarly situated might be expected to possess, control, or know.

(q) "Manufacture" means to produce or manufacture in the United States or import into the customs territory of the United States.

(r) "Manufacture or import for commercial purposes" means:

(1) To import, produce, or manufacture with the purpose of obtaining an immediate or eventual commercial advantage for the manufacturer or importer, and includes, among other things, "manufacture" of any amount of a chemical substance or mixture:

(i) For commercial distribution, including for test marketing.

(ii) For use by the manufacturer, including use for product research and development or as an intermediate.

(2) The term also applies to substances that are produced coincidentally during the manufacture, processing, use, or disposal of another substance or mixture, including byproducts that are separated from that other substance or mixture and impurities that remain in that substance or mixture. Byproducts and impurities without separate commercial value are nonetheless produced for the purpose of obtaining a commercial advantage, since they are part of the manufacture of a chemical substance for commercial purposes.

(s) "Manufacture solely for export" means to manufacture or import for commercial purposes a chemical substance solely for export from the United States under the following restrictions on activities in the United States:

(1) Distribution in commerce is limited to purposes of export or processing solely for export as defined in § 721.3 of this chapter.

(2) The manufacturer or importer, and any person to whom the substance is distributed for purposes of export or processing solely for export (as defined in § 721.3 of this chapter), may not use the substance except in small quantities solely for research and development in accordance with § 720.36.

(t) "Manufacturer" means a person who imports, produces, or manufactures a chemical substance. A person who extracts a component chemical substance from a previously existing chemical substance or a complex combination of substances is a manufacturer of that component chemical substance. A person who contracts with a manufacturer to manufacture or produce a chemical substance is also a manufacturer if (1) the manufacturer manufactures or produces the substance exclusively for that person, and (2) that person specifies the identity of the substance and controls the total amount produced and the basic technology for the plant process.

(u) "Mixture" means any combination of two or more chemical substances if the combination does not occur in nature and is not, in whole or in part, the result of a chemical reaction; except "mixture" does include (1) any combination which occurs, in whole or in part, as a result of a chemical reaction if the combination could have been manufactured for commercial purposes without a chemical reaction at the time the chemical substances comprising the combination were combined, and if all of the chemical substances comprising the combination are not new chemical substances, and (2) hydrates of a chemical substance or hydrated ions formed by association of a chemical substance with water, so long as the nonhydrated form is itself not a new chemical substance.

(v) "New chemical substance" means any chemical substance which is not included on the Inventory.

(w) "Nonisolated intermediate" means any intermediate that is not intentionally removed from the equipment in which it is manufactured, in-

cluding the reaction vessel in which it is manufactured, equipment which is ancillary to the reaction vessel, and any equipment through which the chemical substance passes during a continuous flow process, but not including tanks or other vessels in which the substance is stored after its manufacture.

(x) "Person" means any natural person, firm, company, corporation, joint-venture, partnership, sole proprietorship, association, or any other business entity, any State or political subdivision thereof, any municipality, any interstate body, and any department, agency or instrumentality of the Federal Government.

(y) "Possession or control" means in possession or control of the submitter, or of any subsidiary, partnership in which the submitter is a general partner, parent company, or any company or partnership which the parent company owns or controls, if the subsidiary, parent company, or other company or partnership is associated with the submitter in the research, development, test marketing, or commercial marketing of the chemical substance in question. (A parent company owns or controls another company if the parent owns or controls 50 percent or more of the other company's voting stock. A parent company owns or controls any partnership in which it is a general partner). Information is included within this definition if it is:

(1) In files maintained by submitter's employees who are:

(i) Associated with research, development, test marketing, or commercial marketing of the chemical substance in question.

(ii) Reasonably likely to have such data.

(2) Maintained in the files of other agents of the submitter who are associated with research, development, test marketing, or commercial marketing of the chemical substance in question in the course of their employment as such agents.

(z) "Principal importer" means the first importer who, knowing that a new chemical substance will be imported rather than manufactured domestically, specifies the identity of the chemical substance and the total amount to be imported. Only persons who are incorporated, licensed, or doing business in the United States may be principal importers.

(aa) "Process" means the preparation of a chemical substance or mixture, after its manufacture, for distribution in commerce (1) in the same form or physical state as, or in a different form or physical state from, that in which it was received by the person so preparing such substance or mixture, or (2) as part of a mixture or article containing the chemical substance or mixture.

(bb) "Processor" means any person who processes a chemical substance or mixture.

(cc) "Small quantities solely for research and development" (or "small quantities solely for purposes of scientific experimentation or analysis or chemical research on, or analysis of, such substance or another substance, including such research or analysis for the development of a product") means quantities of a chemical substance manufactured, imported, or processed or proposed to be manufactured, imported, or processed solely for research and development that are not greater than reasonably necessary for such purposes.

(dd) "State" means any State of the United States and the District of Columbia, the Commonwealth of Puerto Rico, the Virgin Islands, Guam, the Canal Zone, American Samoa, the Northern Mariana Islands, and any other territory or possession of the United States.

(ee) "Technically qualified individual" means a person or persons (1) who, because of education, training, or experience, or a combination of these factors, is capable of understanding the health and environmental risks associated with the chemical substance which is used under his or her supervision, (2) who is responsible for enforcing appropriate methods of conducting scientific experimentation, analysis, or chemical research to minimize such risks, and (3) who is responsible for the safety assessments and clearances related to the procurement, storage, use, and disposal of the chemical substance as may be appropriate or re-

quired within the scope of conducting a research and development activity.

(ff) "Test data" means data from a formal or informal test or experiment, including information concerning the objectives, experimental methods and materials, protocols, results, data analyses, recorded observations, monitoring data, measurements, and conclusions from a test or experiment.

(gg) "Test marketing" means the distribution in commerce of no more than a predetermined amount of a chemical substance, mixture, or article containing that chemical substance or mixture, by a manufacturer or processor, to no more than a defined number of potential customers to explore market capability in a competitive situation during a predetermined testing period prior to the broader distribution of that chemical substance, mixture, or article in commerce.

(hh) "United States," when used in the geographic sense, means all of the States.

[48 FR 21742, May 13, 1983, as amended at 51 FR 15101, Apr. 22, 1986]

Subpart B—Applicability

§ 720.22 Persons who must report.

(a)(1) Any person who intends to manufacture a new chemical substance in the United States for commercial purposes must submit a notice unless the substance is excluded under § 720.30.

(2) If a person contracts with a manufacturer to manufacture or produce a new chemical substance, and (i) the manufacturer manufactures or produces the substance exclusively for that person, and (ii) that person specifies the identity of the substance, and controls the total amount produced and the basic technology for the plant process, that person must submit the notice. If it is unclear who must report, EPA should be contacted to determine who must submit the notice.

(3) Only manufacturers that are incorporated, licensed, or doing business in the United States may submit a notice.

(b)(1) Any person who intends to import a new chemical substance into the United States for commercial purposes must submit a notice, unless the substance is excluded under § 720.30 or unless the substance is imported as part of an article.

(2) When several persons are involved in an import transaction, the notice must be submitted by the principal importer. If no one person fits the principal importer definition in a particular transaction, the importer should contact EPA to determine who must submit the notice for that transaction.

§ 720.25 Determining whether a chemical substance is on the Inventory.

(a) A new chemical substance is a chemical that is not on the Inventory.

(b)(1) A chemical substance is listed on the Inventory by specific chemical name if its identity is not confidential. If its identity is confidential, it is listed by specific name in the confidential portion of the Inventory. The confidential chemical substance is also listed on the public Inventory by a generic name which masks the specific identity. A person who intends to manufacture or import a chemical substance not listed on the Inventory by specific chemical name may ask EPA whether the substance is included on the confidential Inventory. EPA will answer such an inquiry only if EPA determines that the person has a *bona fide* intent to manufacture or import the chemical substance for commercial purposes.

(2) To establish a *bona fide* intent to manufacture or import a chemical substance, the person who proposes to manufacture or import the substance must submit to EPA:

(i) The specific chemical identity of the substance that the person intends to manufacture or import.

(ii) A signed statement that the person intends to manufacture or import that chemical substance for commercial purposes.

(iii) A description of the research and development activities conducted to date, and the purpose for which the person will manufacture or import the chemical substance.

(iv) An elemental analysis.

(v) Either an X-ray diffraction pattern (for inorganic substances), a mass spectrum (for most other substances),

or an infrared spectrum of the particular chemical substance, or if such data do not resolve uncertainties with respect to the identity of the chemical substance, additional or alternative spectra or other data to identify the substance.

(3) If an importer cannot provide all the information required by paragraph (b)(2) of this section because it is claimed confidential business information by its foreign manufacturer or supplier, the foreign manufacturer or supplier may supply the information directly to EPA.

(4) EPA will review the information submitted by the proposed manufacturer or importer under this paragraph to determine whether it has a *bona fide* intent to manufacture or import the chemical substance. If necessary, EPA will compare this information either to the information requested for the confidential chemical substance under § 710.7(e)(2)(v) of this chapter or the information requested under § 720.85(b)(3)(iii).

(5) If the proposed manufacturer or importer has shown a *bona fide* intent to manufacture or import the substance, and provide sufficient unambiguous chemical identity information so EPA can make a conclusive determination of the chemical substance's Inventory status, EPA will search the confidential Inventory and inform the proposed manufacturer or importer whether the chemical substance is on the confidential Inventory.

(6) If the chemical substance is found on the confidential Inventory, EPA will notify the person(s) who originally reported the chemical substance that another person has demonstrated a *bona fide* intent to manufacture or import the substance and therefore was told that the chemical substance is on the Inventory.

(7) A disclosure of a confidential chemical identity to a person with a *bona fide* intent to manufacture or import the particular chemical substance will not be considered a public disclosure of confidential business information under section 14 of the Act.

(8) EPA will answer an inquiry on whether a particular chemical substance is on the confidential Inventory within 30 days after receipt of a complete submission under paragraph (b)(2) of this section.

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§ 720.30 Chemicals not subject to notification requirements.

The following substances are not subject to the notification requirements of this part:

(a) Any substance which is not a "chemical substance" as defined in § 720.3(e).

(b) Any mixture as defined in § 720.3(u).[1]

(c) Any new chemical substance which will be manufactured or imported in small quantities solely for research and development under § 720.36.

(d) Any new chemical substance which will be manufactured or imported solely for test-marketing purposes under an exemption granted under § 720.38.

(e) Any new chemical substance manufactured solely for export if, when the substance is distributed in commerce:

(1) The substance is labeled in accordance with section 12(a)(1)(B) of the Act.

(2) The manufacturer knows that the person to whom the substance is being distributed intends to export it or process it solely for export as defined in § 721.3 of this chapter.

(f) Any new chemical substance which is manufactured or imported under the terms of a rule promulgated under section 5(h)(4) of the Act.

(g) Any byproduct if its only commercial purpose is for use by public or private organizations that (1) burn it as a fuel, (2) dispose of it as a waste, including in a landfill or for enriching soil, or (3) extract component chemical substances from it for commercial purposes. (This exclusion only applies to the byproduct; it does not apply to

[1] A new chemical substance that is manufactured or imported as part of a mixture is subject to the requirements of this part. This exclusion applies only to a mixture as a whole and not to any chemical substances which are part of the mixture.

the component substances extracted from the byproduct.)

(h) The chemical substances described below: (Although they are manufactured for commercial purposes under the Act, they are not manufactured for distribution in commerce as chemical substances per se and have no commercial purpose separate from the substance, mixture, or article of which they are a part.)

(1) Any impurity.

(2) Any byproduct which is not used for commercial purposes.

(3) Any chemical substance which results from a chemical reaction that occurs incidental to exposure of another chemical substance, mixture, or article to environmental factors such as air, moisture, microbial organisms, or sunlight.

(4) Any chemical substance which results from a chemical reaction that occurs incidental to storage or disposal of another chemical substance, mixture, or article.

(5) Any chemical substance which results from a chemical reaction that occurs upon end use of another chemical substance, mixture, or article such as an adhesive, paint, miscellaneous cleanser or other housekeeping product, fuel additive, water softening and treatment agent, photographic film, battery, match, or safety flare, and which is not itself manufactured or imported for distribution in commerce or for use as an intermediate.

(6) Any chemical substance which results from a chemical reaction that occurs upon use of curable plastic or rubber molding compounds, inks, drying oils, metal finishing compounds, adhesives, or paints, or any other chemical substance formed during the manufacture of an article destined for the marketplace without further chemical change of the chemical substance except for those chemical changes that occur as described elsewhere in this paragraph.

(7) Any chemical substance which results from a chemical reaction that occurs when (i) a stabilizer, colorant, odorant, antioxidant, filler, solvent, carrier, surfactant, plasticizer, corrosion inhibitor, antifoamer or defoamer, dispersant, precipitation inhibitor, binder, emulsifier, deemulsifier, dewatering agent, agglomerating agent, adhesion promoter, flow modifier, pH neutralizer, sequesterant, coagulant, flocculant, fire retardant, lubricant, chelating agent, or quality control reagent functions as intented, or (ii) a chemical substance, which is intended solely to impart a specific physiochemical characteristic, functions as intended.

(8) Any nonisolated intermediate.

(i) Any chemical substance which is manufactured solely for non-commercial research and development purposes. Non-commercial research and development purposes include scientific experimentation, research, or analysis conducted by academic, government, or independent not-for-profit research organizations (e.g., universities, colleges, teaching hospitals, and research institutes), unless the activity is for eventual commercial purposes.

[48 FR 21742, May 13, 1983, as amended at 51 FR 15101, Apr. 22, 1986]

§ 720.36 Exemption for research and development.

(a) This part does not apply to a chemical substance if the following conditions are met:

(1) The chemical substance is manufactured or imported only in small quantities solely for research and development.

(2) The manufacturer or importer notifies all persons in its employ or to whom it directly distributes the chemical substance, who are engaged in experimentation, research, or analysis on the chemical substance, including the manufacture, processing, use, transport, storage, and disposal of the substance associated with research and development activities, of any risk to health, identified under paragraph (b) of this section, which may be associated with the substance. The notification must be made in accordance with paragraph (c) of this section.

(3) The chemical substance is used by, or directly under the supervision of, a technically qualified individual.

(b)(1) To determine whether notification under paragraph (a)(2) of this section is required, the manufacturer or importer must review and evaluate the following information to deter-

mine whether there is reason to believe there is any potential risk to health which may be associated with the chemical substance:

(i) Information in its possession or control concerning any significant adverse reaction by persons exposed to the chemical substance which may reasonably be associated with such exposure.

(ii) Information provided to the manufacturer or importer by a supplier or any other person concerning a health risk believed to be associated with the substance.

(iii) Health and environmental effects data in its possession or control concerning the substance.

(iv) Information on health effects which accompanies any EPA rule or order issued under sections 4, 5, or 6 of the Act that applies to the substance and of which the manufacturer or importer has knowledge.

(2) When the research and development activity is conducted solely in a laboratory and exposure to the chemical substance is controlled through the implementation of prudent laboratory practices for handling chemical substances of unknown toxicity, and any distribution, except for purposes of disposal, is to other such laboratories for further research and development activity, the information specified in paragraph (b)(1) of this section need not be reviewed and evaluated. (For purposes of this paragraph, a laboratory is a contained research facility where relatively small quantities of chemical substances are used on a non-production basis, and where activities involve the use of containers for reactions, transfers, and other handling of substances designed to be easily manipulated by a single individual.)

(c)(1) The manufacturer or importer must notify the persons identified in paragraph (a)(2) of this section by means of a container labeling system, conspicuous placement of notices in areas where exposure may occur, written notification to each person potentially exposed, or any other method of notification which adequately informs persons of health risks which the manufacturer or importer has reason to believe may be associated with the substance, as determined under paragraph (b)(1) of this section.

(2) If the manufacturer or importer distributes a chemical substance manufactured or imported under this section to persons not in its employ, the manufacturer or importer must in written form:

(i) Notify those persons that the substance is to be used only for research and development purposes.

(ii) Provide the notice of health risks specified in paragraph (c)(1) of this section.

(3) The adequacy of any notification under this section is the responsibility of the manufacturer or importer.

(d) A chemical substance is not exempt from reporting under this part if any amount of the substance, including as part of a mixture, is processed, distributed in commerce, or used, for any commercial purpose other than research and development, except where the chemical substance is processed, distributed in commerce, or used only as an impurity or as part of an article.

(e) Quantities of the chemical substance, or of mixtures or articles containing the chemical substance, remaining after completion of research and development activities may be:

(1) Disposed of as a waste in accordance with applicable Federal, state, and local regulations, or

(2) Used for the following commercial purposes:

(i) Burning it as a fuel.

(ii) Reacting or otherwise processing it to form other chemical substances for commercial purposes, including extracting component chemical substances.

(f) Quantities of research and development substances existing solely as impurities in a product or incorporated into an article, in accordance with paragraph (d) of this section, and quantities of research and development substances used solely for commercial purposes listed in paragraph (e) of this section, are not subject to the requirements of paragraphs (a), (b), and (c) of this section, once research and development activities have been completed.

(g) A person who manufactures or imports a chemical substance in small

quantities solely for research and development is not required to comply with the requirements of this section if the person's exclusive intention is to perform research and development activities solely for the purpose of determining whether the substance can be used as a pesticide.

[51 FR 15102, Apr. 22, 1986]

§ 720.38 Exemptions for test marketing.

(a) Any person may apply for an exemption to manufacture or import a new chemical substance for test marketing. EPA may grant the exemption if the person demonstrates that the chemical substance will not present an unreasonable risk to injury to health or the environment as a result of the test marketing.

(b) Persons applying for a test-marketing exemption should provide the following information:

(1) All existing data regarding health and environmental effects of the chemical substance, including physical/chemical properties or, in the absence of such data, a discussion of toxicity based on structure-activity relationships (SAR) and relevant data on chemical analogues.

(2) The maximum quantity of the chemical substance which the applicant will manufacture or import for test marketing.

(3) The maximum number of persons who may be provided the chemical substance during test marketing.

(4) The maximum number of persons who may be exposed to the chemical substance as a result of test marketing, including information regarding duration and route of such exposures.

(5) A description of the test-marketing activity, including its length and how it can be distinguished from full-scale commercial production and research and development.

(c) In accordance with section 5(h)(6) of the Act, after EPA receives an application for exemption under this section, the Agency will file with the Office of the Federal Register a notice containing a summary of the information provided in the application, to the extent it has not been claimed confidential.

(d) No later than 45 days after EPA receives an application, the Agency will either approve or deny the application. Thereafter, EPA will publish a notice in the FEDERAL REGISTER explaining the reasons for approval or denial.

(e) In approving an application for exemption, EPA may impose any restrictions necessary to ensure that the substance will not present an unreasonable risk of injury to health and the environment as a result of test marketing.

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Subpart C—Notice Form

§ 720.40 General.

(a) *Use of the notice form.* Each person who is required by Subpart B to submit a notice must complete, sign, and submit a notice containing the information in the form and manner set forth in EPA Form No. 7710-25 [2] under Appendix A of this part. Except as otherwise provided in Subpart C, each notice must be submitted with all referenced attachments. The information on the form and all attachments (unless the attachment appears in the open scientific literature) must be in English. All information submitted must be true and correct.

(b) *When to submit a notice.* Each person who is required to submit a notice must submit the notice at least 90 calendar days before manufacture or import of the new chemical substance for commercial purposes begins.

(c) *Where to submit a notice.* Each person who submits a notice must submit it to the address listed on the notice form.

(d) *General notice requirements.* Each person who submits a notice must provide the information described in § 720.45 and specified on the notice form, to the extent such information is known to or reasonably as-

[2] Copies may be obtained from: Industry Assistance Office (TS-799), Office of Toxic Substances, Environmental Protection Agency, 401 M St., SW., Washington, DC 20460.

certainable by the submitter. In accordance with § 720.50, the notice must also include any test data in the submitter's possession or control and descriptions of other data which are known to or reasonably ascertainable by the submitter and which concern the health and environmental effects of the new chemical substance.

(e) *Agency or joint submissions.* (1) A manufacturer or importer may designate an agent to submit the notice. Both the manufacturer or importer and the agent must sign the certification on the form.

(2) A manufacturer or importer may authorize another person, (e.g., a foreign manufacturer or supplier, or a toll manufacturer) to report some of the information required in the notice to EPA on its behalf. If separate portions of a joint notice are not submitted together, the submitter should indicate which information will be supplied by another person and identify that person. The other person must submit the information on the appropriate part of the notice form. The manufacturer or importer and any other person supplying the information must sign the certification provided on their respective notice forms.

(3) If EPA receives a submission which does not include information required by this rule, which the submitter indicates that it has authorized another person to provide, the notice review period will not begin until EPA receives that information.

(f) *New information.* During the notice review period, if the submitter possesses, controls, or knows of new information that materially adds to, changes, or otherwise makes significantly more complete the information included in the notice, the submitter must that information to the address listed on the notice form within ten days of receiving the new information, but no later than five days before the end of the notice review period. The new submission must clearly identify the submitter and the notice to which the new information is related. If the new information becomes available during the last five days of the notice review period, the submitter must immediately inform its EPA contract for that notice by telephone.

(g) *Chemical substances subject to a section 4 test rule.* (1) Except as provided in paragraph (g)(3) of this section, if (i) A person intends to manufacture or import a new chemical substance which is subject to the notification requirements of this part, and (ii) The chemical substance is subject to a test rule promulgated under section 4 of the Act before the notice is submitted, section 5(b)(1) of the Act requires the person to submit the test data required by the testing rule with the notice. The person must submit the data in the form and manner specified in the test rule and in accordance with § 720.50. If the person does not submit the test data, the submission is incomplete and EPA will follow the procedures in § 720.65.

(2) If EPA has granted the submitter an exemption under section 4(c) of the Act from the requirement to conduct tests and submit data, the submitter may not submit a notice until EPA receives the test data.

(3) If EPA has granted the submitter an exemption under section 4(c) of the Act and if another person previously has submitted the test data to EPA, the exempted person may either submit the test data or provide the following information as part of the notice:

(i) The name, title, and address of the person who submitted the test data to EPA.

(ii) The date the test data were submitted to EPA.

(iii) A citation for the test rule.

(iv) A description of the exemption and a reference identifying it.

(h) *Chemical substances subject to a section 5(b)(4) rule.* (1) If a person (i) intends to manufacture or import a new chemical substance which is subject to the notification requirements of this part and which is subject to a rule issued under section 5(b)(4) of the Act; and (ii) is not required by a rule issued under section 4 of the Act to submit test data for the substance before the submission of a notice, the person must submit to EPA data described in paragraph (h)(2) of this section at the time the notice is submitted.

(2) Data submitted under paragraph (h)(1) of this section must be data

which the person submitting the notice believes show that the manufacture, processing, distribution in commerce, use and disposal of the substance, or any combination of such activities, will not present an unreasonable risk of injury to health or the environment.

(Approved by the Office of Management and Budget under control number 2070-0012)

§ 720.45 Information that must be included in the notice form.

Each person who submits a notice must include the information specified in the notice form to the extent it is known to or reasonably ascertainable by the submitter. However, no person is required to include information which relates solely to exposure of human or ecological populations outside of the United States. The notice form requires the following information relating to the manufacture, processing, distribution in commerce, use, and disposal of the new chemical substance:

(a)(1) For substances whose composition can be represented by a definite structural diagram (Class 1 substances), the notice must provide the chemical name (preferably Chemical Abstracts Service (CAS) or International Union of Pure and Applied Chemistry (IUPAC) nomenclature), the molecular formula, CAS Registry Number (if available), and a structural diagram.

(2) For chemical substances that cannot be fully represented by a structural diagram (Class 2 substances), the notice must provide the chemical name, the CAS Registry Number (if available), and molecular formula. The notice must identify the immediate precursors and reactants by name and CAS Registry Number (if the number is available). The notice must include a partial or incomplete structural diagram if possible. Chemical names for such substances should be developed according to the guidelines in the TSCA Chemical Substance Inventory, Initial Inventory, Volume 1.

(3) For polymers, the notice must identify monomers and other reactants used in the manufacture of the polymer by chemical name and CAS Registry Number (if available). The notice must indicate the typical percent of each monomer and other reactant in the polymer (by weight percent of total polymer); the maximum residual of each monomer present in the polymer; and a partial or incomplete structural diagram, if possible. The notice must provide estimates of the minimum number-average molecular weight of the polymer and the amount of low weight species below 500 and below 1,000 molecular weight and describe how the estimates were obtained.

(b) The impurities anticipated to be present in the substance by name, CAS Registry number, and weight percent of the total substance.

(c) Known synonyms or trade names of the new chemical substance.

(d) A description of the byproducts resulting from the manufacture, processing, use, and disposal of the new chemical substance.

(e) The estimated maximum amount to be manufactured or imported during the first year of production and the estimated maximum amount to be manufactured or imported during any 12-month period during the first three years of production.

(f) A description of intended categories of use by function and application, the estimated percent of production volume devoted to each category of use, and the percent of the new substance in the formulation for each commercial or consumer use.

(g) For sites controlled by the submitter:

(1) The identity of sites where the new substance will be manufactured, processed, or used.

(2) A process description of each manufacture, processing, and use operation which includes a diagram of the major unit operations and chemical conversions, the identity and entry point of all feedstocks, and the points of release of the new chemical substance.

(3) Worker exposure information, including worker activities, physical form of the new substance to which workers may be exposed, the number of workers, and the duration of activities.

(4) Information on release of the new substance to the environment, including the quantity and media of release and type of control technology used.

(h) For sites not controlled by the submitter, a description of each type of processing and use operation involving the new chemical substance, including identification of the estimated number of processing or use sites, situations in which worker exposure to and/or environmental release of the new chemical substance will occur, the number of workers exposed and the duration of exposure, and controls which limit worker exposure and environmental release.

§ 720.50 Submission of test data and other data concerning the health and environmental effects of a substance.

(a) *Test data on the new chemical substance in the possession or control of the submitter.* (1) Except as provided in paragraph (d) of this section, each notice must contain all test data in the submitter's possession or control which are related to the effects on health or the environment of any manufacture, processing, distribution in commerce, use, or disposal of the new chemical substance or any mixture or article containing the new chemical substance, or any combination of such activities. This includes test data concerning the new chemical substance in a pure, technical grade, or formulated form.

(2) A full report or standard literature citation must be submitted for the following types of test data:

(i) Health effects data.

(ii) Ecological effects data.

(iii) Physical and chemical properties data.

(iv) Environmental fate characteristics.

(v) Monitoring data and other test data related to human exposure to or environmental release of the chemical substance.

(3)(i) If the data do not appear in the open scientific literature, the submitter must provide a full report. A full report includes the experimental methods and materials, results, discussion and data analysis, conclusions, references and the name and address of the laboratory that developed the data.

(ii) If the data appear in the open scientific literature, the submitter need only provide a standard literature citation. A standard literature citation includes author, title, periodical name, date of publication, volume, and page numbers.

(4)(i) If a study, report, or test is incomplete when a person submits a notice, the submitter must identify the nature and purpose of the study; name and address of the laboratory developing the data; progress to date; types of data collected; significant preliminary results; and anticipated completion date.

(ii) If a test or experiment is completed before the notice review period ends, the person must submit the study, report, or test to the address listed on the notice form, as specified in paragraph (a)(3)(i) of this section, within ten days of receiving it, but no later than five days before the end of the review period. If the test or experiment is completed during the last five days of the review period, the submitter must immediately inform its EPA contact for that notice by telephone.

(5) For test data in the submitter's possession or control which are not listed in paragraph (a)(2) of this section, a person is not required to submit a complete report. The person must submit a summary of the data. If EPA so requests, the person must submit a full report within ten days of the request, but no later than five days before the end of the review period.

(6) All test data described by paragraph (a) are subject to these requirements, regardless of their age, quality, or results.

(b) *Other data concerning the health and environmental effects of the new chemical substance that are known to or reasonably ascertainable by the submitter.* (1) Except as provided in paragraph (d) of this section, any person who submits a notice must describe the following data, including any data from a health and safety study, if the data are related to the effects on health or the environment of any manufacture, processing, distribution in commerce, use, or disposal of the new chemical substance, of any mix-

ture or article containing the new chemical substance, or of any combination of such activities:

(i) Any data, other than test data, in the submitter's possession or control.

(ii) Any data, including test data, which are not in the submitter's possession or control, but which are known to or reasonably ascertainable by the submitter. For the purposes of this section, data are known to or reasonably ascertainable by the submitter if the data are known to any of its employees or other agents who are associated with the research and development, test marketing, or commercial marketing of the substance.

(2) Data that must be described include data concerning the new chemical substance in a pure, technical grade, or formulated form.

(3) The description of data reported under this paragraph must include:

(i) If the data appear in the open scientific literature, a standard literature citation, which includes the author, title, periodical name, date of publication, volume, and pages.

(ii) If the data are not contained in the open scientific literature, a description of the type of data and summary of the results, if available, and the names and addresses of persons the submitter believes may have possession or control of the data.

(4) All data described by this paragraph are subject to these requirements, regardless of their age, quality, or results; and regardless of whether they are complete at the time the notice is submitted.

(c) [Reserved]

(d) *Data that need not be submitted*—(1) *Data previously submitted to EPA.* (i) A person need not submit any data previously submitted to EPA with no claims of confidentiality if the notice includes the office or person to whom the data were submitted, the date of submission, and, if appropriate, a standard literature citation as specified in paragraph (a)(3)(ii) of this section.

(ii) For data previously submitted to EPA with a claim of confidentiality, the person must resubmit the data with the notice and any claim of confidentiality, under § 720.80.

(2) *Efficacy data.* This part does not require submission of any data related solely to product efficacy. This does not exempt a person from submitting any of the data specified in paragraph (a), (b), or (c) of this section.

(3) *Non-U.S. exposure data.* This part does not require submission of any data which relates only to exposure of humans or the environment outside the United States. This does not exclude nonexposure data such as data on health effects (including epidemiological studies), ecological effects, physical and chemical properties, or environmental fate characteristics.

[48 FR 21742, May 13, 1983, as amended at 51 FR 15102, Apr. 22, 1986]

§ 720.57 Imports.

(a) Except as otherwise provided in this section, the provisions of this Subpart C apply to each person who submits a notice for a new chemcial substance which he or she intends to import for a commercial purpose. In addition, each importer must comply with this section.

(b) EPA will hold the principal importer, or the importer that EPA determines must submit the notice when there is no principal importer under § 720.22(b)(2), liable for complying with this part, for completing the notice form and for the completeness and truthfulness of all information which it submits.

Subpart D—Disposition of Notices

§ 720.60 General.

This subpart establishes procedures that EPA will follow in reviewing notices.

§ 720.62 Notice that notification is not required.

When EPA receives a notice, EPA will review it to determine whether the chemical substance is subject to the requirements of this part. If EPA determines that the chemical substance is not subject to these requirements, EPA will notify the submitter that section 5 of the Act does not prevent the manufacture or import of the

substance and that the submission is not a notice under this part.

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§ 720.65 Acknowledgment of receipt of a notice; errors in the notice; incomplete submissions; false and misleading statements.

(a) *Notification to submitter.* EPA will acknowledge receipt of each notice by sending the submitter a letter that identifies the premanufacture notice number assigned to the new chemical substance and the date on which the review period begins. The review period will begin on the date the notice is received by the Office of Toxic Substances Document Control Officer. The acknowledgment does not constitute a finding by EPA that the notice, as submitted, is in compliance with this part.

(b) *Errors in the notice.* (1) Within 30 days of receipt of the notice, EPA may request that the submitter remedy errors in the notice. The following are examples of such errors:

(i) Failure to date the notice form.

(ii) Typographical errors that cause data to be misleading or answers to any questions to be unclear.

(iii) Contradictory information.

(iv) Ambiguous statements or information.

(2) In the request to correct the notice, EPA will explain the action which the submitter must take to correct the notice.

(3) If the submitter fails to correct the notice within 15 days of receipt of the request, EPA may extend the notice period under section (5)(c) of the Act, in accordance with § 720.75(c).

(c) *Incomplete submissions.* (1) A submission is not complete, and the notification period does not begin, if:

(i) The wrong person submits the notice form.

(ii) The submitter does not sign the notice form.

(iii) Some or all of the information in the notice or the attachments are not in English, except for published scientific literature.

(iv) The submitter does not use the notice form.

(v) The submitter does not provide information that is required by section 5(d)(1)(B) and (C) of the Act and § 720.50.

(vi) The submitter does not provide information required on the notice form and by § 720.45 or indicate that it is not known to or reasonably ascertainable by the submitter.

(vii) The submitter does not submit a second copy of the submission with all confidential information deleted for the public file, as required by § 720.80(b)(2).

(viii) The submitter does not include any information required by section 5(b)(1) of the Act and pursuant to a rule promulgated under section 4 of the Act, as required by § 720.40(g).

(ix) The submitter does not submit data which the submitter believes show that the chemical substance will not present an unreasonable risk of injury to health or the environment, if EPA has listed the chemical substance under section 5(b)(4) of the Act, as required in § 720.40(h).

(2)(i) If EPA receives an incomplete submission, the Director, or his or her delegate, will notify the submitter within 30 days of receipt that the submission is incomplete and that the notice review period will not begin until EPA receives a complete notice.

(ii) If EPA obtains additional information during the notice review period that indicates the original submission was incomplete, the Director, or his or her delegate, may declare the submission incomplete within 30 days after EPA obtains the additional information and so notify the submitter.

(3) The notification that a submission is incomplete under paragraph (c)(2) (i) or (ii) of this section will include:

(i) A statement of the basis of EPA's determination that the submission is incomplete.

(ii) The requirements for correcting the incomplete submission.

(iii) Information on procedures under paragraph (c)(4) of this section for filing objections to the determination or requesting modification of the requirements for completing the submission.

(4) Within ten days after receipt of notification by EPA that a submission

is incomplete, the submitter may file written objections requesting that EPA accept the submission as a complete notice or modify the requirements necessary to complete the submission.

(5)(i) EPA will consider the objections filed by the submitter. The Director, or his or her delegate, will determine whether the submission was complete or incomplete, or whether to modify the requirements for completing the submission. EPA will notify the submitter in writing of EPA's response within ten days of receiving the objections.

(ii) If the Director, or his or her delegate, determines, in response to the objection, that the submission was complete, the notice review period will be deemed suspended on the date EPA declared the notice incomplete, and will resume on the date that the notice is declared complete. The submitter need not correct the notice as EPA originally requested. If EPA can complete its review within 90 days from the date of the original submission, the Director, or his or her delegate, may inform the submitter that the running of the review period will resume on the date EPA originally declared it incomplete.

(iii) If the Director, or his or her delegate, modifies the requirements for completing the submission or concurs with EPA's original determination, the notice review period will begin when EPA receives a complete notice.

(d) *Materially false or misleading statements.* If EPA discovers at any time that person submitted materially false or misleading statements in the notice, EPA may find that the notice was incomplete from the date it was submitted, and take any other appropriate action.

§ 720.70 Notice in the Federal Register.

(a) *Filing of* FEDERAL REGISTER *notice.* In accordance with section 5(d)(2) of the Act, after EPA receives a notice, EPA will file with the Office of the Federal Register a notice including the information specified in paragraph (b) of this section.

(b) *Contents of notice.* (1) In the public interest, the specific chemical identity listed in the notice will be published in the FEDERAL REGISTER unless the submitter has claimed chemical identity confidential. If the submitter claims confidentiality, a generic name will be published in accordance with § 720.85(a)(3).

(2) The categories of use of the new chemical substance will be published as reported in the notice unless this information is claimed confidential. If confidentiality is claimed, the generic information which is submitted under § 720.87(b) will be published.

(3) A list of data submitted in accordance with § 720.50(a) will be published. In addition, for test data submitted in accordance with § 720.40(g), a summary of the data will be published.

(4) The submitter's identity will be published, unless the submitter has claimed it confidential.

§ 720.75 Notice review period.

(a) *Length of notice review period.* The notice review period specified in section 5(a) of the Act runs for 90 days from the date the Document Control Officer for the Office of Toxic Substances receives a complete notice, or the date EPA determines the notice is complete under § 720.65(c), unless the Agency extends the period under section 5(c) of TSCA and paragraph (c) of this section.

(b) *Suspension of the running of the notice review period.* (1) A submitter may voluntarily suspend the running of the notice review period if the Director or his or her delegate agrees. If the Director does not agree, the review period will continue to run, and EPA will notify the submitter. A submitter may request a suspension at any time during the notice review period. The suspension must be for a specified period of time.

(2) A request for suspension may be made in writing to the TSCA Document Processing Center (TS-790), Rm. L-100, Office of Toxic Substances, Environmental Protection Agency, 401 M St., SW., Washington, DC 20460. The suspension also may be made orally, including by telephone, to the submitter's EPA contact for that notice. EPA will send the submitter a written con-

firmation that the suspension has been granted.

(i) An oral request may be granted for 15 days only. To obtain a longer suspension, the Document Control Officer for the Office of Toxic Substances must receive written confirmation of the oral request. The notice review period is suspended as of the date of the oral request.

(ii) If the submitter has not made a previous oral request, the running of the notice review period is suspended as of the date of receipt of the written request by the Document Control Officer for the Office of Toxic Substances.

(c) *Extension of notice review period.* (1) At any time during the notice review period, EPA may determine that good cause exists to extend the notice review period specified in paragraph (a) of this section.

(2) If EPA makes such a determination, EPA will:

(i) Notify the submitter that EPA is extending the notice review period for a specified length of time, and state the reasons for the extension.

(ii) Issue a notice for publication in the FEDERAL REGISTER which states that EPA is extending the notice review period and gives the reasons for the extension.

(3) The initial extension may be for a period of up to 90 days. If the initial extension is for less than 90 days, EPA may make additional extensions. However, the total period of extensions may not exceed 90 days for any notice.

(4) The following are examples of situations in which EPA may find that good cause exists for extending the notice review period:

(i) EPA has reviewed the notice and determined that there is a significant possibility that the chemical substance will be regulated under section 5(e) or section 5(f) of the Act, but EPA is unable to initiate regulatory action within the initial 90-day period.

(ii) EPA has reviewed the submission and is seeking additional information.

(iii) EPA has received significant additional information during the notice review period.

(iv) The submitter has failed to correct a notice after receiving EPA's request under § 720.65(b).

(d) *Notice of expiration of notice review period.* EPA will notify the submitter that the notice review period has expired or that EPA has completed its review of the notice. Expiration of the review period does not constitute EPA approval or certification of the new chemical substance, and does not mean that EPA may not take regulatory action against the substance in the future. After expiration of the statutory notice review period, in the absence of regulatory action by EPA under section 5(e), 5(f), or 6(a) of the Act, the submitter may manufacture or import the chemical substance even if the submitter has not received notice of expiration.

(e) *Withdrawal of a notice by the submitter.* (1) A submitter may withdraw a notice during the notice review period. A statement of withdrawal must be made in writing to the TSCA Document Processing Center (TS-790), Rm. L-100, Office of Toxic Substances, Environmental Protection Agency, 401 M St., SW., Washington, DC 20460. The withdrawal is effective upon receipt of the statement by the Document Control Officer.

(2) If a manufacturer or importer which withdrew a notice later resubmits a notice for the same chemical substance, a new notice review period begins.

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[48 FR 21742, May 13, 1983, as amended at 53 FR 12523, Apr. 15, 1988]

§ 720.78 Recordkeeping.

(a) Any person who submits a notice under this part must retain documentation of information in the notice, including (1) other data, as defined in § 720.50(b), in the submitter's possession or control; and (2) records of production volume for the first three years of production or import, the date of commencement of manufacture or import, and documentation of this information. This information must be retained for five years from the date of commencement of manufacture of import.

(b)(1) Persons who manufacture or import a chemical substance under

§ 720.36 must retain the following records:

(i) Copies of, or citations to, information reviewed and evaluated under § 720.36(b)(1) to determine the need to make any notification of risk.

(ii) Documentation of the nature and method of notification under § 720.36(c)(1) including copies of any labels or written notices used.

(iii) Documentation of prudent laboratory practices used instead of notification and evaluation under § 720.36(b)(2).

(iv) The names and addresses of any persons other than the manfacturer or importer to whom the substance is distributed, the identity of the substance to the extent known, the amount distributed, and copies of the notifications required under § 720.36(c)(2). These records are not required when substances are distributed as impurities or incorporated into an article, in accordance with paragraph (d) of this section.

(2) A person who manufactures or imports a chemical substance under § 720.36 and who manufactures or imports the substance in quantities greater than 100 kilograms per year must retain records of the identity of the substance to the extent known, the production volume of the substance, and the person's disposition of the substance. The person is not required to maintain records of the disposition of products containing the substance as an impurity or of articles incorporating the substances.

(3) Records under this paragraph must be retained for 5 years after they are developed.

(c) Any person who obtains a test-marketing exemption under this part must retain documentation of information in the application and documentation of compliance with any restrictions imposed by EPA when it granted the application. This information must be retained for five years from the final date of manufacture or import under the exemption.

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[48 FR 21742, May 13, 1983; 48 FR 33872, July 26, 1983, as amended at 51 FR 15102, Apr. 22, 1986]

Subpart E—Confidentiality and Public Access to Information

§ 720.80 General provisions.

(a) A person may assert a claim of confidentiality for any information which he or she submits to EPA under this part.

(b) Any claim of confidentiality must accompany the information when it is submitted to EPA.

(1)(i) For information submitted on the notice form, the claim(s) must be asserted on the form in the manner prescribed on the notice form.

(ii) When a person submits information in an attachment, the claim(s) must be asserted in the attachment as described on the notice form.

(2) The person must submit two copies of each notice form and any attachments if any information is claimed confidential.

(i) One copy of the form and attachments must be complete. In that copy, the submitter must mark the information which is claimed confidential in the manner prescribed on the notice form.

(ii) The second copy must be complete except that all information claimed as confidential in the first copy must be deleted. EPA will place the second copy in the public file.

(iii) If the submitter does not provide the second copy, the submission is incomplete and the notice review period does not begin to run until EPA receives the second copy, in accordance with § 720.65(c)(1)(vi).

(c) EPA will disclose information that is subject to a claim of confidentiality asserted under this section only to the extent permitted by the Act, this subpart, and Part 2 of this title.

(d) If a notice submitter does not assert a claim of confidentiality for information at the time it is submitted to EPA, EPA may make the information public and place it in the public file without further notice to the submitter.

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§ 720.85 Chemical identity.

(a) *Claims applicable to the period prior to commencement of manufacture or import.* (1)(i) A person who submits information to EPA under this part may assert a claim of confidentiality for the chemical identity of the new chemical substance. This claim will apply only to the period prior to the commencement of manufacture or import for commercial purposes. A submitter may assert this claim only if the submitter believes that public disclosure prior to commencement of manufacture or import of the fact that anyone intends to manufacture or import the specific chemical substance for commercial purposes would reveal confidential business information.

(ii) If the notice includes a health and safety study concerning the new chemical substance and if the claim for confidentiality with respect to the chemical identity is denied in accordance with § 720.90(c), EPA will deny a claim asserted under this paragraph.

(2) Any person who asserts a claim of confidentiality for chemical identity under this paragraph must provide one of the following items at the time the notice is submitted:

(i) The generic name which was accepted by EPA in the prenotice consultation conducted under paragraph (a)(3) of this section.

(ii) One generic name that is only as generic as necessary to protect the confidential chemical identity of the particular chemical substance. The name should reveal the specific chemical identity to the maximum extent possible. The generic name will be subject to EPA review and approval at the time a notice of commencement is submitted.

(3)(i) Any person who intends to assert a claim of confidentiality for the chemical identity of a new chemical substance may seek a determination by EPA of an appropriate generic name for the substance before submitting a notice. For this purpose, the person should submit to EPA:

(A) The chemical identity of the substance.

(B) A proposed generic name(s) which in only as generic as necessary to protect the confidential chemical identity of the new chemical substance. The name(s) should reveal the chemical identity of the substance to the maximum extent possible.

(ii) Within 30 days, EPA will inform the submitter either that one of the proposed generic names is adequate or that none is adequate and further consultation is necessary.

(4) If a submitter claims chemical identity to be confidential under this paragraph, and if the submitter complies with paragraph (a)(2) of this section, EPA will issue for publication in the FEDERAL REGISTER notice described in § 720.70 the generic name proposed by the submitter or one agreed upon by EPA and the submitter.

(b) *Claims applicable to the period after commencement of manufacture or import.* (1) Any claim of confidentiality under paragraph (a) of this section is applicable only until the substance is manufactured or imported for commercial purposes and becomes eligible for inclusion on the Inventory. To maintain the confidential status of the chemical identity when the substance is added to the Inventory, a submitter must reassert the confidentiality claim and substantiate the claim in the notice of commencement of manufacture required uner § 720.102. A submitter may not claim the chemical indentity confidential for the period after commencement of manufacture or import unless the submitter claimed the chemical identity confidential for the period prior to commencement of manufacture or import under paragraph (a) of this section.

(2)(i) A person who believes that public disclosure of the fact that anyone manfactures or imports the new chemical substance for commercial purposes would reveal confidential business information may assert a claim of confidentiality under this paragraph.

(ii) If the notice includes a health and safety study concerning the new chemical substance, and if the claim for confidentiality with respect to the chemical identity is denied in accordance with § 720.90(c), EPA will deny a claim asserted under this paragraph.

(3) Any person who asserts a confidentiality claim for chemical identity must:

(i) Comply with the requirements of paragraph (a)(3) of this section regarding submission of a generic name.

(ii) Agree that EPA may disclose to a person with a *bona fide* intent to manufacture or import the chemical substance the fact that the particular chemical substance is included on the confidential Inventory for purposes of notification under section 5(a)(1)(A) of the Act.

(iii) Have available for the particular chemical substance, and agree to furnish to EPA upon request:

(A) An elemental analysis.

(B) Either an X-ray diffraction pattern (for inorganic substances), a mass spectrum (for most other substances), or an infrared spectrum of the particular chemical substance, or if such data do not resolve uncertainties with respect to the identity of the chemical substance, additional or alternative spectra or other data to identify the chemical substance.

(iv) Provide a detailed written substantiation of the claim, by answering the following questions:

(A) What harmful effects to your competitive position, if any, do you think would result if EPA publishes on the Inventory the identity of the chemical substance? How could a competitor use such information given the fact that the identity of the substance otherwise would appear on the Inventory of chemical substances with no link between the substance and your company or industry? How substantial would the harmful effects of disclosure be? What is the casual relationship between the disclosure and the harmful effects?

(B) For what period of time should confidential treatment be given? Until a specific date, the occurrence of a specific event, or permanently? Why?

(C) Has the chemical substance been patented? If so, have you granted licenses to others with respect to the patent as it applies to the chemical substance? If the chemical substance has been patented and therefore disclosed through the patent, why should it be treated as confidential for purposes of the Inventory?

(D) Has the identity of the chemical substance been kept confidential to the extent that your competitors do not know it is being manufactured on imported for a commercial purpose by anyone?

(E) Is the fact that someone is manufacturing or importing this chemical substance for commercial purposes available to the public, e.g., in technical journals or other publications; in libraries; or in State, local, or Federal agency public files?

(F) What measures have you taken to prevent undesired disclosure of the fact that you are manufacturing or importing this substance for a commercial purpose?

(G) To what extent has the fact that you are manufacturing or importing this chemical substance for a commercial purpose been disclosed to others? What precautions have you taken in regard to these disclosures? Has this information been disclosed to the public or to competitors?

(H) In what form does this particular chemical substance leave the site of manufacture, e.g., as part of a product; in an effluent or emission stream? If so, what measures have you taken to guard against discovery of its identity?

(I) If the chemical substance leaves the site of manufacture in a product that is available to either the public or your competitors, can they identify the substance by analyzing the product?

(J) For what purpose do you manufacture or import the substance?

(K) Has EPA, another Federal agency, or any Federal court made any pertinent confidentiality determinations regarding this chemical substance? If so, copies of such determinations must be included in the substantiation.

(L) If the notice includes a health and safety study concerning the new chemical substance, the submitter must also answer the questions in § 720.90(b)(2).

(4) If the submitter does not meet the requirements of this paragraph, EPA will deny the claim of confidentiality.

(5)(i) EPA will publish a generic name on the public Inventory if:

(A) The submitter asserts a claim of confidentiality in accordance with this paragraph.

(B) No claim for confidentiality of the specific chemical identity as part of a health and safety study has been denied in accordance with Part 2 of this Title or § 720.90.

(ii) Publication of a generic name on the public Inventory does not create a category for purposes of the Inventory. Any person who has a *bona fide* intent to manufacture or import a chemical substance which is described by a generic name on the public Inventory may submit an inquiry to EPA under § 720.25(b) to determine whether the particular chemical substance is included on the confidential Inventory.

(iii) Upon receipt of a request described in § 720.25(b), EPA may require the submitter which originally asserted confidentiality for a chemical substance to submit to EPA the information listed in paragraph (b)(3)(iii) of this section.

(iv) Failure to submit any of the information required under paragraph (b)(3)(iii) of this section within ten days of a request by EPA under this paragraph is a waiver of the original submitter's confidentiality claim. In this event, EPA may place the specific chemical identity on the public Inventory without further notice to the original submitter.

(6) If a submitter asserts a claim of confidentiality under this paragraph, EPA will examine the generic chemical name proposed by the submitter.

(i) If EPA determines that the generic name proposed by the submitter is only as generic as necessary to protect the confidential identity of the particular chemical substance, EPA will place that generic name on the public Inventory.

(ii) If EPA determines that the generic name proposed by the submitter is more generic than necessary to protect the confidential identity, EPA will propose in writing, for review by the submitter, an alternative generic name that will reveal the chemical identity of the chemical substance to the maximum extent possible.

(iii) If the generic name proposed by EPA is acceptable to the submitter, EPA will place that generic name on the public Inventory.

(iv) If the generic name proposed by EPA is not acceptable to the submitter, the submitter must explain in detail why disclosure of that generic name would reveal confidential business information and propose another generic name which is only as generic as necessary to protect the confidential identity. If EPA does not receive a response from the submitter within 30 days after the submitter receives the proposed name, EPA will place EPA's chosen generic name on the public Inventory. If the submitter does provide the information requested, EPA will review the response. If the submitter's proposed generic name is acceptable, EPA will publish that generic name on the public Inventory. If the submitter's proposed generic name is not acceptable, EPA will notify the submitter of EPA's choice of a generic name. Thirty days after this notification, EPA will place the chosen generic name on the public Inventory.

§ 720.87 Categories or proposed categories of uses of a new chemical substance.

(a) A person who submits information to EPA under this Part on the categories or proposed categories of use of a new chemical substance may assert a claim of confidentiality for this information.

(b) A submitter that asserts such a claim must:

(1) Report the categories or proposed categories of use of the chemical substance.

(2) Provide, in nonconfidential form, a description of the uses that is only as generic as necessary to protect the confidential business information. The generic use description will be included in the FEDERAL REGISTER notice described in § 720.70.

(c) The person must submit the information required by paragraph (b) of this section in the manner specified in the notice form.

§ 720.90 Data from health and safety studies.

(a) *Information other than specific chemical identity.* Except as provided in paragraph (b) of this section, EPA

will deny any claim of confidentiality with respect to information included in a health and safety study, unless the information would disclose confidential business information concerning:

(1) Processes used in the manufacture or processing of a chemical substance or mixture.

(2) In the case of a mixture, the portion of the mixture comprised by any of the chemical substances in the mixture.

(3) Informaton which is not in any way related to the effects of a substance on human health or the environment, such as the name of the submitting company, cost or other financial data, product development or marketing plans, and advertising plans, for which the person submits a claim of confidentiality in accordance with § 720.80.

(b) *Specific chemical identity*—(1) *Claims applicable to period prior to commencement of manufacture.* A claim of confidentiality for the period prior to commencement of manufacture or import for the chemical identity of a chemical substance for which a health and safety study was submitted must be asserted in conjunction with a claim asserted under § 720.85(a).

(2) *Claims applicable to period after commencement of manufacture or import for commercial purposes.* To maintain the confidential status of the chemical identity of a chemical substance for which a health and safety study was submitted after commencement of manufacture or import, the claim must be reasserted and substantiated in conjunction with a claim under § 720.85(b). In addition to the questions set forth in § 720.85(b)(3)(iv) of this part, the submitter must answer the following questions:

(i) Would disclosure of the chemical identity disclose processes used in the manufacture or processing of a chemical substance or mixture? Describe how this would occur. In responding to the question in § 720.85(b)(3)(iv)(A), explain what harmful competitive effects would occur from disclosure of this process information.

(ii) Would disclosure of the chemical identity disclose the portion of a mixture comprised by any of the substances in the mixture? Describe how this would occur. In responding to the question in § 720.85(b)(3)(iv)(A), explain what harmful competitive effects would occur from disclosure of this information.

(iii) Do you assert that disclosure of the chemical identity is not necessary to interpret any of the health and safety studies you have submitted? If so, explain how a less specific identity would be sufficient to interpret the studies.

(c) *Denial of confidentiality claim.* EPA will deny a claim of confidentiality for chemical identity under paragraph (b) of this section, unless:

(1) The information would disclose processes used in the manufacture or processing of a chemical substance or mixture.

(2) In the case of a mixture, the information would disclose the portion of the mixture comprised by any of the substances in the mixture.

(3) The specific chemical identity is not necessary to interpret a health and safety study.

(d) *Use of generic names.* When EPA discloses a health and safety study containing a specific chemical identity, which the submitter has claimed confidential, and if the Agency has not denied the claim under paragraph (c) of this section, EPA will identify the chemical substance by the generic name selected under § 720.85.

(Approved by the Office of Management and Budget under control number 2070-0012)

§ 720.95 Public file.

All information submitted with a notice, including any health and safety study and other supporting documentation, will become part of the public file for that notice, unless such materials are claimed confidential. In addition, EPA may add materials to the public file, subject to subpart E of this part. Any of the nonconfidential material described in this subpart will be available for public inspection in the TSCA Public Docket Office, Rm. NE-G004, 401 M St., SW., Washington, DC, between the hours of 8 a.m. and 4 p.m. weekdays, excluding legal holidays.

[48 FR 21742, May 13, 1983, as amended at 53 FR 12523, Apr. 15, 1988]

Subpart F—Commencement of Manufacture or Import

§ 720.102 Notice of commencement of manufacture or import.

(a) *Applicability.* Any person who commences the manufacture or import of a new chemical substance for a non-exempt commercial purpose for which that person previously submitted a section 5(a) notice under this part must submit a notice of commencement of manufacture or import.

(b) *When to report.* (1) If manufacture or import for commercial purposes begins on or after the effective date of this rule, the submitter must submit the notice to EPA on, or no later than 30 calendar days, after the first day of such manufacture or import.

(2) If manufacture or import for commercial purposes began or will begin before the effective date of this rule, the submitter must submit the notice by the effective date of this rule.

(c) *Information to be reported.* The notice must contain the following information: Specific chemical identity, premanufacture notice number, and the date when manufacture or import commences. If the person claimed chemical identity confidential in the commencement notice, and wants the identity to be listed on the confidential Inventory, the claim must be reasserted and substantiated in accordance with § 720.85(b). Otherwise, EPA will list the specific chemical identity on the public Inventory.

(d) *Where to submit.* Notices of commencement of manufacture or import should be submitted to: TSCA Document Processing Center (TS-790), Rm. L-100, Office of Toxic Substances, Environmental Protection Agency, 401 M St., SW., Washington, DC 20460.

(Approved by the Office of Management and Budget under control number 2070-0012)

[48 FR 21742, May 13, 1983, as amended at 48 FR 41140, Sept. 13, 1983; 51 FR 15103, Apr. 22, 1986; 53 FR 12523, Apr. 15, 1988]

Subpart G—Compliance and Inspections

§ 720.120 Compliance.

(a) Failure to comply with any provision of this part is a violation of section 15 of the Act (15 U.S.C 2614).

(b) A person who manufactures or imports a new chemical substance before a notice is submitted and the notice review period expires is in violation of section 15 of the Act even if that person was not requied to submit the notice under § 720.22.

(c) Using for commercial purposes a chemical substance or mixture which a person knew or had reason to know was manufactured, processed, or distributed in commerce in violation of section 5 of this rule is a violation of section 15 of the Act (15 U.S.C. 2614).

(d) Failure or refusal to establish and maintain records or to permit access to or copying of records, as required by the Act, is a violation of section 15 of the Act (15 U.S.C. 2614).

(e) Failure or refusal to permit entry or inspection as required by section 11 is a violation of section 15 of the Act (15 U.S.C. 2614).

(f) Violators may be subject to the civil and criminal penalties in section 16 of the Act (15 U.S.C. 2615) for each violation. Persons who submit materially misleading or false information in connection with the requirements of any provision of this rule may be subject to penalties calculated as if they never filed their notices.

(g) EPA may seek to enjoin the manufacture or processing of a chemical substance in violation of this rule or act to seize any chemical substance manufactured or processed in violation of this rule or take other actions under the authority of section 7 of this Act (15 U.S.C. 2606) or section 17 or this Act (15 U.S.C. 2616).

§ 720.122 Inspections.

EPA will conduct inspections under section 11 of the Act to assure compliance with section 5 of the Act and this rule, to verify that information submitted to EPA under this rule is true and correct, and to audit data submitted to EPA under this rule.

APPENDIX A—PREMANUFACTURE NOTICE FOR NEW CHEMICAL SUBSTANCES

O.M.B. No. 2070-0012: Approval Expires 3-3-86

EPA United States Environmental Protection Agency

PREMANUFACTURE NOTICE FOR NEW CHEMICAL SUBSTANCES

When completed send this form to:

DOCUMENT CONTROL OFFICER
OFFICE OF TOXIC SUBSTANCES, TS-793
U.S. E.P.A.
401 M STREET, SW
WASHINGTON, D.C. 20460

AGENCY USE ONLY

Date of receipt

Enter the total number of pages in the Premanufacture Notice ——→

Document control number | EPA case number

GENERAL INSTRUCTIONS

You must provide all information requested in this form to the extent that it is known to or reasonably ascertainable by you. Make reasonable estimates if you do not have actual data.

Before you complete this form, you should read the "Instructions Manual for Premanufacture Notification" (Instructions Manual).

Part I. GENERAL INFORMATION

You must provide the chemical identity of the new chemical substance, even if you claim the identity as confidential. You may authorize another person to submit the identity for you, but your submission will not be complete and review will not begin until EPA receives this information.

Part II. HUMAN EXPOSURE AND ENVIRONMENTAL RELEASE

You may need additional copies of part II, sections A and B if there are several manufacture, processing, or use operations that you will describe in the notice. You should reproduce these sections as needed.

Part III. LIST OF ATTACHMENTS

You should attach additional sheets if you do not have enough space on the form to answer a question fully. In part III, list these attachments, any test data or other data, and any optional information that you include in the notice.

OPTIONAL INFORMATION

You may include in the notice any information that you want EPA to consider in evaluating the new substance. The Instructions Manual identifies categories of optional information that you may want EPA to review.

CONFIDENTIALITY CLAIMS

You may claim any information in this notice as confidential. To assert a claim on the form, mark (X) the confidential box next to the information that you claim as confidential. To assert a claim in an attachment, circle or bracket the information you claim as confidential. If you claim information in the notice as confidential, you must provide a sanitized version of the notice, including attachments, to EPA with your submission. For additional instructions on claiming information as confidential, read the Instructions Manual.

Indicate below the categories of information you have claimed as confidential in the notice.

1 ☐ SUBMITTER IDENTITY
2 ☐ CHEMICAL IDENTITY
3 ☐ PRODUCTION VOLUME
4 ☐ USE INFORMATION
5 ☐ PROCESS INFORMATION
6 ☐ PORTIONS OF A MIXTURE
7 ☐ OTHER INFORMATION

TEST DATA AND OTHER DATA

You are required to submit all test data in your possession or control and to provide a description of all other data known to or reasonably ascertainable by you if these data are related to the health and environmental effects of the manufacture, processing, distribution in commerce, use, or disposal of the new chemical substance. Standard literature citations may be submitted for data in the open scientific literature. Complete test data, not summaries of data, must be submitted if they do not appear in the open literature. Following are examples of test data and other data. You should submit these data according to the requirements of §720.50 of the Premanufacture Notification Rule (40 CFR Part 720).

Test data

- **Environmental fate data**
  - Spectra (UV, visible, and infrared)
  - Density of liquids and solids
  - Water solubility
  - Melting point/melting range
  - Boiling point/boiling range
  - Vapor pressure
  - Partition coefficient, n-octanol/water
  - Biodegradation
  - Hydrolysis (as a function of pH)
  - Photochemical degradation
  - Adsorption/desorption to soil types
  - Dissociation constant
  - Other physical/chemical properties
- **Health effects data**
  - Mutagenicity
  - Carcinogenicity
  - Teratogenicity
  - Acute toxicity
  - Repeated dose toxicity
  - Metabolism studies
  - Sensitization
  - Irritation
- **Environmental effects data**
  - Microbial and algal toxicity
  - Terrestrial vascular plant toxicity (e.g., seed germination studies, growth inhibition)
  - Acute and chronic toxicity to animals (e.g., fish, birds, mammals, invertebrates)

Other data

- **Risk assessments**
- **Structure/activity relationships**
- **Test data not in the possession or control of the submitter**

EPA Form 7710-25 (4-26-83)

CERTIFICATION

I certify that to the best of my knowledge and belief:

1. The company named in part I, section A, subsection 1a of this notice form intends to manufacture or import for a commercial purpose, other than in small quantities solely for research and development, the substance identified in part I, section B.
2. All information provided in this notice is complete and truthful as of the date of submission.
3. I am submitting with this notice all test data in my possession or control and a description of all other data known to or reasonably ascertainable by me as required by § 720.50 of the Premanufacture Notification Rule.

		Confidential
Signature of authorized official	Date	
Signature of agent — *(If applicable)*	Date	

Part I — GENERAL INFORMATION

Section A — SUBMITTER IDENTIFICATION

Mark (X) the "Confidential" box next to any subsection you claim as confidential.

				Confidential
1a. Person submitting notice	Name of authorized official	Title		
	Company			
	Mailing address (number and street)			
	City, State, ZIP code			
b. Agent *(if applicable)*	Name of authorized official	Title		
	Company			
	Mailing address (number and street)			
	City, State, ZIP code			
c. *If you are submitting this notice as part of a joint submission, mark (X) this box.* → ☐				
2. Technical contact	Name	Title		
	Company			
	Mailing address (number and street)			
	City, State, ZIP code	Telephone: Area code	Number	
3. If you have had a prenotice communication (PC) concerning this notice and EPA assigned a PC Number to the notice, enter the number →			*Mark (X) if none* → ☐	
4. If you have submitted a test-marketing exemption (TME) application for the chemical substance covered by this notice, enter the TME number assigned by EPA →			*Mark (X) if none* → ☐	
5. If you have submitted a bona fide request for the chemical substance covered by this notice, enter the bona fide request number assigned by EPA →			*Mark (X) if none* → ☐	

6. Type of Notice — *Mark (X)* 1 ☐ Manufacture 2 ☐ Import

Part I — GENERAL INFORMATION — Continued

Section B — CHEMICAL IDENTITY INFORMATION

Mark (X) the "Confidential" box next to any item you claim as confidential.

Complete either item 1 or 2 as appropriate. Complete all other items.

If another person will submit chemical identity information for you, mark (X) the box at the right. → ☐

Identify the name, company, and address of that person in a continuation sheet.

Confidential

1. Class 1 or 2 chemical substances (for definitions of class 1 and class 2 substances, see the Instructions Manual)

a. Class of substance — *Mark (X)* 1 ☐ Class 1 2 ☐ Class 2

b. Chemical name (preferably CAS or IUPAC nomenclature)

c. Molecular formula and CAS Registry Number (if known)

d. For a class 1 substance, provide a structural diagram. For a class 2 substance — (1) List the immediate precursor substances with their respective CAS Registry Numbers. (2) Describe the nature of the reaction or process. (3) Indicate the range of composition and the typical composition (where appropriate). (4) Provide a representative structural diagram (if possible).

☐ *Mark (X) this box if you attach a continuation sheet.*

Part I — GENERAL INFORMATION — Continued

Section B — CHEMICAL IDENTITY INFORMATION — Continued

2. Polymers (For a definition of polymer, see the Instructions Manual.)

Confidential

a. Indicate the lowest number-average molecular weight composition of the polymer you intend to manufacture. Indicate the maximum weight percent of low molecular weight species below 500 and below 1,000 absolute molecular weight of that composition. Describe the methods of measurement or the bases for your estimates.

☐ *Mark (X) this box if you attach a continuation sheet.*

b. You must make separate confidentiality claims for monomer or other reactant identity, composition information, and residual information. Mark (X) the "Confidential" box next to any item you claim as confidential.

(1) — Provide the chemical name and CAS Registry Number of each monomer or other reactant used in the manufacture of the polymer.
(2) — Indicate the typical weight percent of each monomer or other reactant in the polymer.
(3) — Mark (X) the identity column if you want a monomer or other reactant used at two weight percent or less to be listed as part of the polymer description on the TSCA Chemical Substance Inventory.
(4) — Indicate the maximum weight percent of each monomer or other reactant that may be present as a residual in the polymer as manufactured for commercial purposes.

Monomer or other reactant and CAS Registry Number (1)	Confidential	Typical composition (2)	Identity Mark (X) (3)	Confidential	Maximum residual (4)	Confidential
		%			%	
		%			%	
		%			%	
		%			%	
		%			%	
		%			%	
		%			%	

☐ *Mark (X) this box if you attach a continuation sheet.*

c. Provide a representative structural diagram of the polymer, if possible.

☐ *Mark (X) this box if you attach a continuation sheet.*

Part I — GENERAL INFORMATION — Continued

Section B — CHEMICAL IDENTITY INFORMATION — Continued

3. Impurities

(a) — Identify each impurity that may be reasonably anticipated to be present in the chemical substance as manufactured for commercial purposes. Provide the CAS Registry Number if available. If there are unidentified impurities, enter "unidentified."
(b) — Estimate the maximum weight percent of each impurity. If there are unidentified impurities, estimate their total weight percent.

Impurity and CAS Registry Number (a)	Maximum percent (b)	Confidential
	%	
	%	
	%	
	%	
	%	
	%	
	%	

☐ *Mark (X) this box if you attach a continuation sheet.*

4. Synonyms — Enter any synonyms for the new chemical substance identified in subsection 1 or 2. — Confidential

☐ *Mark (X) this box if you attach a continuation sheet.*

5. Trade identification — List trade names for the new chemical substance identified in subsection 1 or 2.

☐ *Mark (X) this box if you attach a continuation sheet.*

6. Generic chemical name — If you claim chemical identity as confidential, enter the generic chemical name that you developed with EPA during prenotice communication. If you have not developed a generic name with EPA, provide a generic name that reveals the specific chemical identity of the new chemical substance to the maximum extent possible. Read the TSCA Chemical Substance Inventory, Initial Inventory, Volume I for guidance on developing generic names.

☐ *Mark (X) this box if you attach a continuation sheet.*

7. Byproducts — Describe any byproducts resulting from the manufacture, processing, use, or disposal of the new chemical substance at sites you control. Provide the CAS Registry Number if available.

Byproduct (1)	CAS Registry Number (2)	Confidential

☐ *Mark (X) this box if you attach a continuation sheet.*

Part I— GENERAL INFORMATION — Continued

Section C — PRODUCTION, IMPORT, AND USE INFORMATION

Mark (X) the "Confidential" box next to any item you claim as confidential.

1. Production volume — Estimate the maximum production volume during the first 12 months of production. Also estimate the maximum production volume for any consecutive 12-month period during the first three years of production.

Maximum first 12-month production (kg/yr)	Maximum 12-month production (kg/yr)	Confidential

2. Use information

You must make separate confidentiality claims for the description of the category of use, the percent of production volume devoted to each category, the formulation of the new substance, and other use information. Mark (X) the "Confidential" box next to any item you claim as confidential.

a. (1) — Describe each intended category of use of the new chemical substance by function and application.
(2) — Estimate the percent of total production for the first three years devoted to each category of use.
(3) — Estimate the percent of the new substance as formulated in mixtures, suspensions, emulsions, solutions, or gels as manufactured for commercial purposes at sites under your control associated with each category of use.
(4) — Mark (X) whether the use is site-limited, industrial, commercial, or consumer. Mark more than one column if appropriate.
Read the Instructions Manual for examples.

Category of use (1)	Confidential	Production (percent) (2)	Confidential	Formulation (percent) (3)	Confidential	Mark (X) appropriate column(s) (4) Site-limited	Industrial	Commercial	Consumer	Confidential
		%		%						
		%		%						
		%		%						
		%		%						

☐ *Mark (X) this box if you attach a continuation sheet.*

b. Generic use description — If you claim any category of use description in subsection 2a as confidential, enter a generic description of that category. Read the Instructions Manual for examples of generic use descriptions.

☐ *Mark (X) this box if you attach a continuation sheet.*

3. Hazard information — Include in the notice a copy or reasonable facsimile of any hazard warning statement, label, material safety data sheet, or other information which will be provided to any person regarding protective equipment or practices for the safe handling, transport, use, or disposal of the new chemical substance. List in part III any hazard information you include.

☐ *Mark (X) this box if you attach hazard information.*

Part II — HUMAN EXPOSURE AND ENVIRONMENTAL RELEASE

Section A — INDUSTRIAL SITES CONTROLLED BY THE SUBMITTER

Complete section A for each type of manufacture, processing, or use operation involving the new chemical substance at industrial sites you control.

Mark (X) the "Confidential" box next to any item you claim as confidential.

1. Operation description

a. Identity – Enter the identity of the site at which the operation will occur.

	Confidential
Name	
Site address (number and street)	
City, County, State, ZIP code	
If the same operation will occur at more than one site, enter the number of sites. → Identify the additional sites on a continuation sheet.	
☐ *Mark (X) this box if you attach a continuation sheet.*	

b. Type – *Mark (X)*

1 ☐ Manufacturing 2 ☐ Processing 3 ☐ Use

c. Amount and Duration – *Complete 1 or 2 as appropriate*

1. Batch	Maximum kg/batch	Hours/batch	Batches/year
2. Continuous	Maximum kg/day	Hours/day	Days/year

d. Process description

(1) Diagram the major unit operation steps and chemical conversions.

(2) Provide the identity, the approximate weight (by kg/day or kg/batch), and entry point of all feedstocks (including reactants, solvents, and catalysts).

(3) Identify by number the points of release to the environment of the new chemical substance.

☐ *Mark (X) this box if you attach a continuation sheet.*

Part II — HUMAN EXPOSURE AND ENVIRONMENTAL RELEASE — Continued

Section A — INDUSTRIAL SITES CONTROLLED BY THE SUBMITTER — Continued

2. Occupational Exposure

You must make separate confidentiality claims for the description of worker activity, physical form of the new chemical substance, number of workers exposed, and duration of activity. Mark (X) the "Confidential" box next to any item you claim as confidential.

(1) — Describe the activities in which workers may be exposed to the new chemical substance. Include activities in which workers wear protective equipment.
(2) — Indicate the physical form(s) of the new chemical substance at the time of exposure.
(3) — Estimate the maximum number of workers involved in each activity.
(4) and (5) — Estimate the maximum duration of the activity for any worker in hours per day and days per year.

Worker activity (1)	Confidential	Physical form(s) (2)	Confidential	Maximum number (3)	Confidential	Maximum duration		Confidential
						Hrs/day (4)	Days/yr (5)	

☐ *Mark (X) this box if you attach a continuation sheet.*

3. Environmental Release and Disposal

You must make separate confidentiality claims for the release number and the amount of the new chemical substance released and other release and disposal information. Mark (X) the "Confidential" box next to each item you claim as confidential.

(1) — Enter the number of each release point identified in the process description, part II, section A, subsection 1d(3).
(2) — Estimate the amount of the new chemical substance released directly to the environment or into control technology (in kg/day or kg/batch).
(3) — Identify the media (air, land, or water) to which the new substance will be released from that release point.
(4) — Describe control technology, if any, that will be used to limit the release of the new substance to the environment. For releases disposed of on land, characterize the disposal method.
(5) — Identify the destination(s) of releases to water.

Release Number (1)	Amount of new substance released (2)	Confidential	Media of release (3)	Control technology (4)	Confidential

(5) Mark (X) the destination(s) of releases to water. 1 ☐ POTW (publicly owned treatment works) 3 ☐ Other — *Specify*
2 ☐ Navigable waterway

☐ *Mark (X) this box if you attach a continuation sheet.*